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(AN UNDERGRADUATE PUBLICATION)

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EDITORIAL

HEALTH INSURANCE

SECTION III

This is the second from last of this series of editorials and in this we are going to deal with the proposed methods of administration and the benefits derived from the act.

Plan—Outline of the Projected Act (continued)

- (a) Administration
 - (i) Dominion
 - (ii) Provincial
 - (iii) Local
- (b) Benefits
 - (i) Medical
 - (ii) Dental
 - (iii) Pharmaceutical
 - (iv) Hospitals
 - (v) Nursing.

(a) ADMINISTRATION

This outline of the administration is intended to indicate the machinery for administration and no effort will be made to outline the financing of the bill which was outlined briefly in Section II (vol. 21, no. 2, pp. 35-38).

(i) *Dominion*—At the Dominion level there is established a dual directing mechanism which consists of the Minister for Pensions and National Health and an advisory body called the National Council on Health Insurance which is a large body consisting of representatives from the provinces and from all the various groups interested in the scheme as outlined below for the Provincial Health

Insurance Commission. The function of this administration shall be the deciding of matters of general policy as to the methods employed in Public Health administration and that sort of thing. The authority of this body lies in the power of the Minister to withhold grants as outlined in the sub-section on organization in Section II.

(ii) *Provincial*—The great bulk of the administration of the actual benefits and the details of administration falls with this and the local agencies.

At this level it is proposed to set up a Health Insurance Commission. Its chairman shall be “a doctor of medicine, regularly qualified, duly licensed and in good standing in the province, having practised medicine for at least ten years”. He is appointed by the lieutenant-governor. The members of the Commission shall consist of the Provincial Health Officer, representatives of the medical and dental professions, pharmacists, hospital authorities, nurses, insured persons, industrial workers, employers, agriculturists and such other persons as the lieutenant-governor from time to time sees fit to include.

The Commission is required to meet at least twice a year and in the interim the Chairman shall carry out necessary duties. The Commission shall be a Corporate body such as a municipality and shall have such legal privileges and liabilities. They shall have the right to set up offices and employ personnel subject to the provisions of the Civil Service Act.

(iii) *Local*—For economic and effective administration it is proposed to divide the province into “Health Insurance Regions” and “Public Health Regions” with due regard for existing boundaries, natural boundaries, hospital facilities, etc. Each of these shall have a central office

called a Regional Office and if it is deemed necessary the Regions so created may be further subdivided into Divisions with Divisional Offices.

In this way a system of offices are set up all responsible to the central office to be situated in the capital of the Province which shall take care of details of the administration of the Act such as the sale and recording of Health Insurance Stamps and Books and the disbursements to local practitioners.

(b) BENEFITS

The aim of this Act is to provide for the entire population of the province adequate medical, surgical, obstetrical, pharmaceutical, hospital and nursing care. The facilities at hand are not adequate. There are at present insufficient doctors, nurses and hospitals and the most acute shortage is seen in the dental profession.

(i) *Medical Benefits*—These include all necessary medical, surgical and obstetrical benefits for the insured individual and his family. The insured man is free to go to his doctor at any time and, on the recommendation of this practitioner, consultant, specialist and ancillary services are available. No mention is made in the Act of Chiropractors and Osteopaths.

(ii) *Dental Benefits*—These shall include preventative as well as reparative and constructive dentistry. As a result of the inadequacy of the resources, children up to sixteen years of age will be given preference and as complete dental treatment as possible. Above this age the treatment is distributed according to its urgency.

(iii) *Pharmaceutical Benefits*—This is to include “proper and sufficient drugs, materials and appliances” as shall be deemed necessary by the practitioner.

These are to be supplied by the druggists according to a standardized formulary.

(iv) *Hospital Benefits*—Hospital care shall include ward accommodation with the privilege of paying the difference for the use of private or semi-private facilities. The hospital, in addition, will be reimbursed for any service rendered to patients in the form of treatments or comforts according to fixed rates. Hospital treatment is available only on practitioner's recommendation. Provision is made that any insured individual who becomes subject to ward treatment in all teaching hospitals shall be liable for "clinical observation". Private and semi-private accommodations do not permit this.

(v) *Nursing Benefits*—Nursing care shall be at the disposal of the practitioner and the bill authorizes the paying of "practical" and incompletely trained nurses when trained personnel is not available.

This completes the discussion of the Act except for the place which the practitioner occupies in the Health Insurance set-up. In this series to date we have avoided contentious opinion as much as possible and have endeavoured to give a simple outline of fact. In the final article to come in the January issue, the place of the doctor under this scheme and some of the changes and aspects of these changes will be discussed.

THE SCHOOL-CHILD'S BREAKFAST

Many a child is scolded for dullness when he should be treated for under-nourishment. In hundreds of homes a "continental" breakfast of a roll and coffee is the rule. If, day after day, a child breaks the night's fast of twelve hours on this scant fare, small wonder that he is listless, nervous, or stupid at school. A happy solution to the problem is Pablum. Pablum furnishes protective factors especially needed by the school-child—especially calcium, iron and the vitamin B complex. The ease with which Pablum can be prepared enlists the mother's cooperation in serving a nutritious breakfast. This palatable cereal requires no further cooking and can be prepared simply by adding milk or water of any desired temperature.

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NOTES ON DESERT SURGERY

MAJOR-GENERAL OGILVIE, R.A.M.C.

PART I

Ladies and Gentlemen:

I feel that I can probably help you best by trying to point out what are the chief differences between civilian surgery in a first-class centre like that at Toronto and surgery as you will meet it in a theatre of war. In what way does a well trained surgeon have to learn again and orientate himself to the conditions he meets in the field?

Before discussing actual surgery it would be well to prepare you for what is perhaps the greatest shock to most keen young doctors when they have joined the Army—that idleness is the chief difficulty they will have to face. If all of us who have been through this war could analyze the way we have spent our time we should probably find that for fifty per cent of it we have been completely idle, for twenty-five per cent of it normally employed, for twenty per cent working at such high pressure that we could hardly keep up with our duties, and for five per cent undergoing periods of sheer terror. It is very easy to think and suggest that this prevailing idleness is the fault of stupidity and lack of forethought on the part of the military authorities. The chief differences between civil medical practice and the medical service of an Army are that in civilian life needs can be foreseen. It is possible to calculate how many hospital beds and how many doctors are adequate to look after the sick and injured of a town of certain size engaged in certain industries. It is quite possible to make adequate provision to meet an unusual epidemic in a country at peace. But in

wartime the medical services must be arranged to meet the maximum possible emergency and this may occur quite suddenly and at unforeseen places. For example, when Rommel broke through in the western desert eighteen months ago and advanced very rapidly towards the Cairo-Alexandria Road, the Middle East Force had to be prepared for the possibility that the Nile Delta and the Suez Canal might fall into his hands and that a fresh defensive line would have to be organized further south supplied from some port in the Red Sea. A hospital with all its equipment cannot be transported at a moment's notice, and to meet this possible emergency a number of hospitals and special surgical centres were transferred from Egypt to Palestine and a new hospital centre was opened on the borders of Sudan and Abyssinia. Rommel was stopped and eventually routed, and these hospital groups, particularly the latter, had months of complete idleness when their only interest was the matching of trained scorpions against each other for small bets and cigarettes. But if these precautions had not been taken, and if Rommel had broken through, the fate of the wounded would have been deplorable and the medical service would very justly have been blamed for it. The first thing, therefore, that you must be prepared to meet is idleness, and the way you stand up to it is very much a test of your quality; it is well to be prepared with some form of study. If during your service you have brought your Anatomy to the pitch of passing the Primary Fellowship

This is a transcription of an address delivered to VIth Year Medicine on November 24th, 1943. It is divided into two parts simply because of length.

or if you have learned Spanish and Russian, your hours of unemployment will not have been wasted.

The second point I would make before proceeding to the discussion of war surgery is that many of you will be employed as regimental medical officers. If you are built in the right mould you can wish for no better job. A good regimental medical officer is a pearl above price. He is only found after much testing and after many rejects but once found a regiment will not part with him for any bribe. Next to the Commanding Officer the doctor is responsible more than any single man for the morale and the efficiency of his battalion. His chief work is done in quiet times. He must learn to know his men, their physical and mental characters, their habits, their families and the way to tackle them. He must get his men to know him or, to put it better, he must sell himself to them as one who is kindly but inexorable, who cannot be tricked into a wangled sick leave but who will meet real illness with sympathy. This knowledge on his part and confidence on theirs is repaid throughout their association. In quiet times he can do much to prevent that wastage from small causes which is one of the chief reasons for lost efficiency, by lessening the incidence of venereal disease, of eye and ear troubles, of painful feet and of desert sores, common complaints which can be averted or cured by fatherly advice and early preventive treatment. In battle his personal study of his men will bear fruit, for one of the problems of warfare today is the psychiatric casualty. It is the price we must pay for drawing our armies from a civilized and educated group of men. When an untried unit goes into action for the first time about thirty per cent of the casualties fall into this class. Of them eighty per cent are normal men who have broken down under a strain

more than they can bear—battle stress augmented by hunger, fatigue and possibly by recent bad news from home. Twenty per cent are individuals of weak psychological makeup who have managed to conceal their inadequacy in civil life but have broken down under the stress of battle conditions. It is one of the most important functions of the good regimental medical officer that, knowing his men, he can sort the first group from the second. The first need no more than sympathetic encouragement and a short period of rest near the line and they will return to their unit as good as ever. The second will never make soldiers and to retain them will only be to endanger the morale of their more normal comrades; they should be sent down the line immediately and transferred to non-combatant duties. The front line battalion of today, drawn from thinking men, purged by trial of its psychological weaklings and backed by a good regimental medical officer is possibly the best fighting machine the world has ever seen, equal to any in attack, better than any in defeat, and incomparable in disaster since it fights from conviction and not from brute instinct.

In the treatment of wounded the medical officer's sole duty is to send his casualties to the rear as quickly as he can, but he can still do much by his encouragement to prevent that mental anxiety which is so large a feature in shock, and by sorting and labelling the serious emergencies to draw the attention of those further back to the cases demanding prior treatment.

Behind a battalion and as far forward as the minimum essentials of good light, reasonable shelter, and temporary security from attack and sudden movement can be arranged, is done the primary surgery of wounds. The site and the circumstances in which this surgery is done will vary in each campaign, and it is well to remember

in this respect that the lessons of experience apply in their entirety only to the particular time, place, and circumstances in which that experience was gained. In the last war there was a sudden transition at about fifteen miles from the trenches from desolation in front to peace behind. In front of this line were naked stems of trees and shell holes full of mud—behind it the crops were growing and the birds were singing, and somewhere about the line were placed the casualty clearing stations in which surgical equipment and supplies not far short of those in civilian practice, could be placed. In the Battle of Britain the patients were wounded within a few miles of a first-class peace-time hospital and the surroundings of the operating teams and the supply of sterile materials were again adequate. In Abyssinia distances were tremendous, the force was tiny and supplies were hard to come by, but because of the distance, the patients remained for some time under the care of the same unit. In the Western Desert the whole picture was governed by the speed of advance or retreat and the difficulties of supply in a stretch of land that had few ports, one road, and no water. It is of desert surgery that I shall speak today.

The Western Desert contains few areas of soft sand such as we have been led to expect in Beau Geste films and it consists almost entirely of illimitable stretches of firm, white sand or rock, with a surface that is navigable in all directions and for any distance by mechanical vehicles of any kind, a landscape that is devoid of landmarks and equally devoid of obstacles. Here, where fast squadrons of armoured fighting vehicles move like fleets on a sandy ocean, where the attacker may infiltrate miles behind his enemy's lines and the defender may hold isolated boxes, there is no line and no limit. In the last war and in England the patient came to

the surgeon; in this war the surgeon must go to the patient.

That mobile surgery was the answer to mobile war was first learned in the hard school of the Western Desert and the present field surgical unit, irreverently known as "Harley Street on the hoof," is the result of experience in the Libyan campaigns. When Wavell went to Bengasi the old system was in existence. Surgical teams consisting of surgeon, anaesthetist and theatre assistant were sent to join the C.C.S.'s, carrying one set of general surgical instruments but expecting all other supplies from their host unit. The C.C.S. proved too immobile to follow the rapid advance of a mechanized Army and the teams were grafted on to field ambulances, where it was found that the surgical equipment and the nursing facilities of these essentially collecting units were quite inadequate for their needs. As a result of this experience was formed the Middle East Field Surgical Unit, a small independent and highly mobile body consisting of a surgeon, an anaesthetist and seven other ranks, two of whom are drivers, moving with its own transport and carrying all the essentials for major surgery of every kind, but simplified to bedrock essentials. The operating equipment consists of a single tent 18 feet by 16, with a smaller tent let into one side as a sterilizing annex, and the whole unit with its equipment and enough sterile material to operate upon a hundred casualties, is carried in one three-ton truck and one fifteen-hundredweight truck. These units formed a fluid surgical reserve at the disposal of the Director of Medical Services of the Army to be used by him in any combination according to the needs of the moment. When a fast armoured column was making a cut-out sweep into the desert a single field surgical unit might be attached to light field ambulances; this unit was

surgically inefficient, for the capacities of one surgeon are soon exhausted, but the best that could be provided for commando work of this kind. The minimum effective surgical group was considered to be two field surgical units with one field transfusion unit attached to them. The field transfusion officer supplied the blood and the plasma, superintended the resuscitation and in a general way took charge of the pre-operative and post-operative wards, and the surgeons worked around the clock in relays. The best arrangement is a series of larger groups so placed that each man can work twenty-four hours and shut down for twenty-four, giving them time to deal with the slighter cases as well as the more severe ones. Whenever more than two surgical units are together, an X-ray is attached to them if possible.

Reviewing our experience in this last campaign I should like to set down for your benefit what in my view are the chief things that an experienced surgeon has to learn afresh when he enters a theatre of war.

1. Firstly, that military surgery is not traumatic surgery in uniform but is part of the science of warfare. Most surgeons if asked what are the aims of military surgery would say to save life, to prevent suffering and to preserve function; but there is one aim far more important than any of these, and that is to win the war. It is a schoolboy's joke that the best way to prevent milk from turning sour is to leave it in the cow. Similarly, the best way to treat wounds is to prevent them, the only way to prevent wounds is to stop the war, and the only way to stop the war is to win it. The aim of the command in any civilized Army such as ours is to give the best possible treatment to the wounded, but if anything is allowed to interfere with military efficiency the lives of the well and the wounded are risked

alike. In modern mechanized warfare efficiency means speed, simplicity and concealment, and with these needs the surgical service must fit in.

Any surgeon versed in traumatic surgery could design an excellent mobile theatre. Many such have been designed, their detailed construction has given great pleasure to engineers, and the presentation of them to departing expeditions is the privilege of millionaires and philanthropic bodies. But such a mobile theatre presents a very obvious target from the air; not a target for guns, for neither side shoots at the Red Cross, but a target for the camera. When the plate is developed at German Intelligence Headquarters the large square patch means preparations for surgery, therefore preparations for casualties, therefore preparations for an attack. Again, an elaborate surgical unit means more transport, and in any difficult advance, particularly the advance of a victorious Army trying desperately to catch up to the enemy in spite of supply difficulties, every tire that can be kept off the road and every gallon of petrol that can be saved for tanks or airplanes is of life or death importance.

The essentials of good surgery in wound treatment are very simple. Chief among them is a good surgeon who can make a right decision. In methods, the really important things are the arrest of hemorrhage, the relief of tension, adequate immobilization of the injured part, and the routine administration of sulfonamides throughout the first five days.

2. Secondly that the clinical picture of wounds caused by projectiles must be learned afresh, just as were the signs and symptoms of appendicitis when we entered the wards. As we learn our peace-time surgery by the bedside so we must learn our war surgery by the side of the stretcher. I know that you are all familiar

with traumatic surgery, with the accidents of road and a factory, but the wounds of warfare are something new. Such wounds may be no more lacerated, but the tissues are devitalized to a very much greater depth by the passage of a high speed body through them. The surgeon can only learn by experience which wounds are dangerous and which are not. Two faults are always apparent in a surgeon new to the theatre of war. First, unnecessary operations on through and through wounds of soft parts. There is no doubt whatever that if such wounds show evidence of deep hemorrhage or any suggestion of infection they must be laid open. But the majority, with immobilization and the routine administration of sulfonamides, do very well and they recover more quickly and with better function than if they are treated surgically. The second mistake is the wrong handling of cases of gas gangrene and gas infection generally, the unnecessary amputation of limbs that might have been saved, the failure to operate on a case that is showing the early signs of toxemia. A study of the problem of gas gangrene in this war shows a lessened incidence and apparently a new outlook. In the last war we believed that most wounds were contaminated with saprophytic organisms only, that staphylococci and streptococci are usually introduced by human agency, and that clostridia of gas gangrene are only common when fighting takes place in areas of heavy cultivation and that when introduced they usually lead to gas gangrene. Researches in the field by the mobile bacteriological laboratories have led us to think that all three groups are quite common as primary flora in a wound, and that the organisms of gas gangrene in particular can be found in forty to fifty per cent of injuries even in such sparsely cultivated terrains as Tunisia. For the development of gas gangrene, three things

are necessary. First, the presence of the causative organism; second, considerable laceration of tissue on which it can thrive; and third, deficient oxygenation, either local due to the injury of an artery, or general due to the loss of large amounts of blood.

From a clinical aspect three varieties of clostridial infection may be recognized: Firstly, the local wound infection. The wound is foul, the characteristic odor of anaerobic infection is detected, and the discharge is a foul brownish serum; but the surrounding tissues are smooth, the limb is painless, and the patient feels well. Culture will isolate the organisms of gas gangrene but the infection has produced no clinical reaction. The importance of such a discovery is that the wound should be cleansed surgically but left widely open, that prophylactic doses of serum should be administered and that the patient's hemoglobin should be brought up to normal by transfusion.

Secondly, gas cellulitis. The organisms multiply on dead tissues and invade connective tissue planes, subcutaneously or between muscles, where they produce swelling, the discharge of gas and often some staining of the skin. The muscle groups are not invaded and the patient, though perhaps pyrexial and complaining of some discomfort in the limb, is not seriously ill. The treatment of this group is immediate relief of tension by free incisions to the extent of the infection, the administration of serum in full doses continued until the wound is clean, and the correction of any blood loss as before.

Thirdly, the true gas gangrene. The organisms invade a group of striated muscles and multiply rapidly within the sheath, producing tension, killing the muscles from end to end, and liberating their toxins which are absorbed into the circulation. The limb rapidly becomes

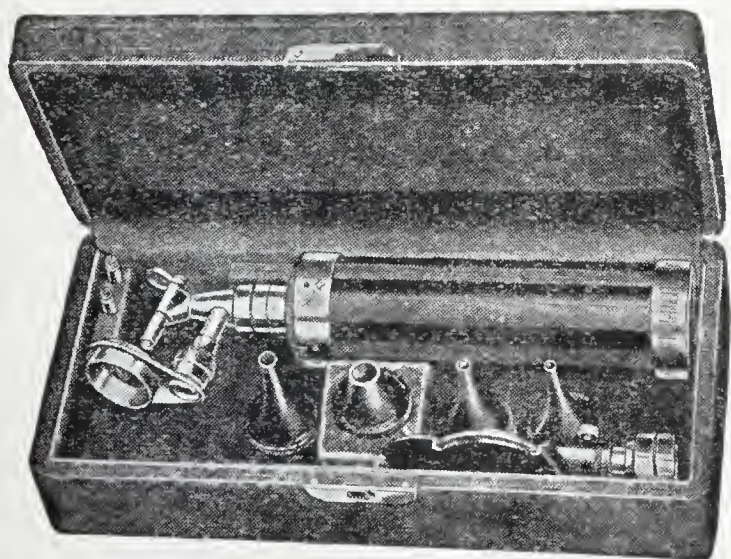
swollen and tympanitic, the skin becomes mottled and later black, and the patient shows all the symptoms of shock—pallor, lassitude, a cold skin, a falling blood pressure and a rising pulse. The treatment in this group is immediate excision of all muscle groups or amputation, whichever appears the simpler. Serums and transfusion are of even greater importance than in the preceding group.

A chief need is to educate all forward surgeons in the clinical features of gas gangrene and still more in recognizing the type of injury in which gas gangrene is liable to develop.

On the first count a surgeon should know that gas is the least important and a not entirely constant feature of gas gangrene. The onset of pain in a limb that has hitherto been comfortable is the first warning sign. In conjunction with this the appearance of the symptoms of shock, the detection of a "dead house" smell, an increase in circumference of the limb, appreciable from half-hour to half-hour, and the discovery of a resonant note when the parts are percussed and a musical hum

when the skin is scraped with a fingernail, should clinch the diagnosis. All reports of deaths from gas gangrene are sent to me, and I have been distressed to find how often the pulse chart shows that the condition should have been apparent two or three days before the surgeon recognized it.

On the second count the forward surgeon should know that wounds such as a laceration of the calf with a ligature of the femoral artery above it, or a laceration of the buttock in a man who has lost three or four pints of blood, are very liable indeed to develop gas gangrene. He should debride these wounds thoroughly, he should leave them widely open, he should replace the lost blood fully by transfusion, he should give the patient a prophylactic dose of serum, and he should tie to his neck the largest label he can find, written in the reddest ink available with the boldest letters he can draw, a warning to all who may subsequently care for him that he must be treated as an urgent case and investigated as a possible gas gangrene.



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A METHOD OF TREATMENT OF THE DIABETIC PATIENT

K. T. G. MOLLER, M.D.

J. R. MCCORRISTON, B.A., M.D., C.M.

We propose to present a concise account of the method of treatment of diabetes mellitus along the lines followed in the wards of the Toronto General Hospital. In this account an attempt will be made to clarify some of the details of treatment of cases of diabetes mellitus so that the student may have a working basis in his mind for the carrying out of this treatment.

Diabetes mellitus is a condition in which, as a result of a deficiency in insulin production, the metabolism of the individual has been altered to such a degree that there arises a relative inability on the part of the tissues to utilize carbohydrate. This deficiency in insulin production leads to a rise in the blood sugar level and when the latter rises above the level of the renal threshold gross glycosuria results. Along with this there may be an increased production of ketone bodies, the blood and tissue levels of which also rise when the rate of their production exceeds the rate of their destruction and excretion. These metabolic changes in the patient lead to the production of classical symptoms and signs varying in severity from those of a symptomless diabetes with minimal signs to those of diabetic coma.

The therapeutic objective, failing the possibility of cure, is the restoration and maintenance of the metabolism of the individual within physiological limits. The patient should have sufficient food to live on, to work on, and be aglycosuric and within normal blood sugar levels.

In order to simplify the discussion we have, on a clinical basis, arbitrarily divided all cases of uncomplicated diabetes into three grades of severity, namely:

1. Mild, with or without classical symptoms
2. Moderately severe — in diabetic acidosis
3. Frank diabetic coma.

ROUTINE FOR A MILD CASE

This case may be symptomless or one with mild typical symptoms. When a diabetic is admitted to hospital a history is taken and a physical examination is made and the following laboratory procedures are carried out:

1. Blood sugar estimation.
2. Carbon dioxide combining power estimation, and serum Rothera test.
3. Complete urinalysis.

Temporarily, while the dietary regimen is being planned, the patient is placed on an admitting diet consisting of:

Protein 36 gm.
Fat 110 gm.
Carbohydrate 30 gm.

The basal caloric requirement is computed from the age and surface area of the body, as estimated from the du Bois chart. Then the proportions of protein, fat and carbohydrate are obtained by using the following formulae:

P equals $\frac{2}{3}$ gm. per kilogram of body weight

C equals $\frac{M - 10P}{30}$

F equals $\frac{10}{M} - \frac{2}{P}$

Where M is the basal caloric requirement for 24 hours.

Whether or not the patient will require insulin is discovered by his progress during the first three or four days on his basal diet. If he becomes aglycosuric

rapidly and has a blood sugar level within the normal limits it is not likely that he will require insulin. On the other hand if there is glycosuria and an abnormally high blood sugar level it is necessary to start the administration of insulin.

In the individual not requiring insulin the diet is increased to caloric levels compatible with his usual activity (maintenance diet) in stages spaced at intervals of three days or more. The usual change at each increase is the addition of 20 gm. of fat and 5 gm. of carbohydrate per day, which means an increase of 200 calories. When protein is to be added to the diet the usual step is 10 gm. of fat and 8 gm. of protein at a time. Protein is increased to about 50 gm. per day in the adult. A few of these patients may require small amounts of insulin to cover the increase in the food intake to the working level.

If, at the end of three or four days on his basal diet, the patient has a blood sugar level above normal, with or without glycosuria, insulin is necessary. As an example, consider a patient who then has a blood sugar level of 160 mgm. per 100 cc. To calculate the amount of insulin required one subtracts 100 from the blood sugar reading and divides the difference by 5, which in this case will be 12. This is the number of units of regular insulin that will be required. This is usually given as 6 units of regular insulin twice a day; one dose one half hour before breakfast, and the other one half hour before supper. When an increase in diet of 20 gm. of fat and 5 gm. of carbohydrate is made, then an addition of 5 to 8 units of regular insulin is given to cover this increase. The diet should be adjusted in this fashion to full caloric requirements of the individual before the change to protamine zinc insulin is made. Regular insulin has a more rapid action, though of shorter duration, than has protamine

zinc insulin, and this permits more frequent adjustments in the diet to be made.

When the patient is stabilized for three or four days with regard to diet and insulin dosage one can make the change to protamine zinc insulin. The dosage of protamine zinc insulin is equal to 60% of the regular insulin dosage when a diet low in carbohydrate is given. On the first morning of the change one supplements the protamine zinc insulin with some regular insulin to cover its latent period. The amount of regular insulin is calculated by taking 60% of the difference between the regular insulin dosage and the dosage of protamine zinc insulin. If, for example, the patient requires 40 units of regular insulin daily, when stabilized, the equivalent dose of protamine zinc insulin will be 60% of 40 which is 24. On the first morning of the change to protamine zinc insulin he should receive also 60% of 16 which is approximately 10 units of regular insulin. Changes are made in the protamine zinc insulin dosage in steps of 2 to 4 units, made not oftener than every 7 days, unless there is gross variation requiring adjustment. Protamine zinc insulin is usually given at any time within 1½ hours before breakfast. In special cases it may also be given at other times.

Before the patient is allowed to go home he should be given certain instructions. The details of the giving of insulin such as boiling the syringe, measuring the insulin accurately, replacing the amount of insulin withdrawn from the vial with an equivalent amount of air and cleansing the skin are all important and should be stressed. He should be informed about the use and the dangers of insulin especially with regard to reactions and acidosis. He should know the early symptoms of the onset of each and be prepared to take the necessary measures

to combat either and if he is in doubt to call a doctor. The patient should be familiar with the management of his diet and he must have scales for the accurate measurement of his food. Instruction in elementary urinalysis, the significance of the results obtained and what to do if abnormal results are obtained should be given the patient. It is also necessary to stress the dangers of infection and the necessity of immediate care of that infection.

Continued observation of this patient after leaving hospital is also very important, especially if his illness has been of short duration. The control of the carbohydrate intake with or without the administration of insulin helps to rest the islet cells of the pancreas thereby allowing a certain amount of repair to take place. In such a patient, a marked improvement may be noted in the carbohydrate tolerance, so much so that it may be possible to discontinue the administration of insulin and allow a fairly large quantity of carbohydrate to be utilized. In diabetics of long standing such improvement is not noted because the majority of the islet cells of the pancreas will have been permanently destroyed. All patients should be seen at regular intervals and necessary adjustments in insulin dosage and diet can be made as required. The diet can be made more palatable by increasing the carbohydrate intake and lowering the amount of fat taken. To do this one substitutes a certain number of grams of carbohydrate for an equal number of grams of fat. Usually there is no increase in the insulin requirement but there is a sacrifice in the caloric intake.

ROUTINE FOR A MODERATELY SEVERE CASE
IN DIABETIC ACIDOSIS

The important findings in such a case are:

Blood sugar.....350 mgm. per 100
cc. + or —
Carbon dioxide combining power
.....35 vol. % + or —
Serum Rothera 2 +
Urinalysis—Sugar 4 +
Acetone 4 +
Some dehydration.

Such a patient requires warmth, absolute bed rest, full nursing care, and the temperature, pulse, blood pressure, and respiratory rate must be followed closely. The initial treatment includes the copious administration of fluids by mouth. These fluids may be water, broths, tea, coffee, orange juice, ginger ale, etc. The patient also receives 25 to 50 units of regular insulin every three to four hours until the state of acidosis has been successfully controlled. The blood sugar estimation should be repeated in 12 hours.

When the state of acidosis and dehydration has been brought under control the patient is placed on a basal diet and given 20 units of regular insulin twice a day. From this point adjustments in diet and insulin dosage are made as for the patient with mild diabetes requiring insulin. Under this plan of treatment the dangers of insulin reaction and of the recurrence of acidosis are avoided because sufficient insulin is given to prevent acidosis and yet not enough to produce hypoglycemia.

ROUTINE FOR A CASE OF FRANK DIABETIC
COMA

The important findings are:
Blood sugar..... 500 mgm. per 100
cc. + or —
Carbon dioxide combining power
.....20 vol. % or less
Serum Rothera 4 +
Urinalysis—Sugar 4 +
Acetone 4 +
Well marked dehydration

Low blood pressure
Subnormal temperature
Patient cannot be roused.

It is evident that this patient requires warmth, bed rest, full nursing care, and that the temperature, pulse, blood pressure and respiratory rate must be followed closely.

The treatment consists in giving 5% glucose in physiological saline intravenously: 1,000 cc. in the first 1½ hours, and another 1,000 cc. in the next three hours, to be followed by 100 to 150 cc. each hour. 100 units of regular insulin are given intravenously at once and repeated two to three hours later. Thereafter 75 units of regular insulin are given twice at three hour intervals. Following this the amount of insulin given depends on the progress of the patient.

Adrenaline, 1 cc. of 1/1,000 solution, is given in each 1,000 cc. of intravenous 5% glucose in saline to help maintain the blood pressure. Pituitrin may also be used if the systolic blood pressure falls below 90 mm. Hg., the dose being 0.25 cc. intravenously and this may be repeated as often as every three minutes if necessary.

Unless the diabetic coma is of short duration and acute onset in all probability the body stores of base will have been depleted by neutralization and excretion of the excess of ketone bodies produced. Therefore sodium bicarbonate is given to help raise the carbon dioxide combining power by replacement of the lost base. The usual amount is 500 cc. of a 5% solution, given intravenously at the rate of 200 cc. per hour. It is necessary to limit its rate of administration since too high a concentration of the sodium ion will cause dilatation of the heart. The blood pressure must be watched and if it drops dangerously low, that is, below 90 mm. Hg. systolic, the sodium bicarbonate must be discontinued.

If the heart rate is excessively rapid, digoxin, 0.3 mgm., may be given in an attempt to reduce its rate to a more efficient one. General supportive measures should be used to combat shock and the low temperature.

It may be added that in diabetic coma all the tissues of the body are in a sense "anesthetised" by the state of acidosis and ketosis. It is well known that if a supply of carbohydrate is available it is metabolised by the tissues in preference to fat and protein. In the untreated diabetic, carbohydrate is not utilized due to the deficiency in the production of insulin and as a result fat is metabolised in large amounts with the excess production of ketone bodies. Hence the aim in treatment of diabetic coma should be to prevent the formation of more ketone bodies by the administration of massive doses of insulin, thereby inducing the metabolism of glucose by preference, and to supply base to neutralize ketone bodies already present. When the state of acidosis has been brought under control treatment can be carried out as outlined above for the patient with mild diabetes. During the first day or so of treatment the patient is allowed to have anything by mouth that he desires in an effort to restore impaired visceral functions, such as peristalsis and excretion of urine. Then he is placed on a basal diet and given 20 units of regular insulin twice a day, and subsequent adjustments are made as required.

SUMMARY

A concise outline for the treatment of diabetes mellitus of three arbitrary degrees of severity has been presented.

ACKNOWLEDGEMENT

We wish to express our sincere gratitude to Dr. W. R. Campbell for his helpful guidance in the preparation of this paper.

THE GLUCOSE TOLERANCE TEST

K. T. G. MOLLER, M.D.

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This test is a method of determining, with a fair degree of certainty, whether or not an individual has diabetes mellitus. It is used in individuals who show glycosuria but have no definite symptoms or other signs and whose blood sugar level is not high enough to be diagnostic. This test should be carried out only in carefully selected cases, that is, those who have a fasting blood sugar below 140 mgm. per 100 cc. With blood sugar levels consistently higher than borderline the test is not indicated and is actually contraindicated because of the danger of temporary or perhaps even permanent reduction of the glucose tolerance.

Diabetes is only one of the numerous causes of glycosuria. A person in whom glycosuria does not recur after two normal meals is not a diabetic and should glycosuria recur it must be established that it is of the hyperglycemic type before the suspicion of diabetes can be further entertained.

The patient is given two normal meals and a urinalysis and a blood sugar estimation are carried out two hours after the second meal. If there is glycosuria and the blood sugar level is 140 mgm. per 100 cc. or over diabetes is present. Absence of glycosuria or hyperglycemia rules out diabetes. The presence of glycosuria without hyperglycemia is suggestive of renal glycosuria or some other non-specific cause. If the history is indefinite and the blood sugar somewhat raised above the normal limit a glucose tolerance test is indicated.

TECHNIQUE OF THE TEST

For three days preceding the test the subject must have eaten at least 100 gm. of carbohydrate each day.

No food may be eaten after 7.00 p.m. of the day preceding the test. Water, beef broth or clear tea is allowed.

At 8.45 a.m. a specimen of urine and a sample of venous blood are taken to determine the presence or absence of sugar in the urine and the fasting blood sugar level.

Between 9.00 and 9.10 a.m. the subject drinks 100 gm. of glucose dissolved in 300 cc. of water flavored with lemon juice.

The bladder is immediately emptied and the specimen is saved and further specimens are collected when samples of blood are taken.

Samples of venous blood are collected at the following times after the test is begun: at $\frac{1}{2}$ hour, at one hour, at two hours, and at three hours. Water may be taken during the test and is particularly of value if the patient has difficulty in voiding small quantities of urine.

The results of the blood sugar estimations are plotted on graph paper, blood glucose level in mgm. per 100 cc. against time, and a curve is drawn through these points.

Urinalysis is done to determine when glycosuria begins, where the renal threshold is, and whether or not renal glycosuria is present.

INTERPRETATION OF THE GLUCOSE TOLERANCE CURVE

Four types of curve are found:

1. Normal—(a) Ideal
(b) Lag
2. High tolerance curve
3. Low tolerance curve.

1. (a) The chief characteristics of the ideal tolerance curve are:
 - a. It starts from a normal fasting

level and reaches its peak in 20-40 minutes.

b. The peak usually falls between 140 and 160 mgm. per 100 cc. for venous blood.

c. The curve returns to a fasting level or below it within two hours.

1. (b) Lag curve: This type of curve rises to a higher peak than the ideal curve, but returns to the fasting level or lower within the normal limit of two hours.

2. High tolerance curve:

a. Fasting blood sugar level is normal or below.

b. The curve does not rise to a normal height and has a flat peak.

c. The curve falls with the normal rapidity and it may fall below the initial level.

3. Low tolerance curve, or diabetic type of curve (so called):

a. Fasting blood sugar level may be normal, but is frequently as high as or higher than the renal threshold which most often lies between 160 and 170 mgm. per 100 cc.

b. The rise in the curve continues longer than normal and it may be an hour or more before the summit is reached.

c. The peak is higher and more rounded.

d. The descent of the curve is prolonged. This is the pathognomonic feature of the "diabetic curve". The extent of this prolongation is roughly proportional to the impairment of the glucose tolerance.

Glycosuria at the end of three hours is a signal for taking further blood sugar tests at 4 and 5 hours. The results obtained when the glucose tolerance test

is performed on an individual will determine the further management of the case and for this reason it is of great importance.

The diabetic curve sometimes occurs with hyperthyroidism, arthritis, liver diseases, in duodenal ulcer, and in advanced arteriosclerosis as well as in certain brain lesions. The clinical picture helps to differentiate these cases.

In a true normal glycosuria does not occur in any of the specimens of urine. In renal glycosuria it may occur in the fasting specimen or at blood sugar levels below the normal threshold accompanying either a normal type or a high tolerance curve. With the lag type of curve glycosuria is of short duration accompanying the excessive rise in blood sugar level but may persist even when the blood sugar level has fallen below the normal threshold.

In diabetes mellitus glycosuria may occur in the fasting specimen accompanying a blood sugar level above the normal renal threshold. In subsequent specimens it may occur when the threshold value is exceeded and even persist once the threshold has been broken through or in mild cases disappear with the fall of the blood sugar below threshold levels. In some severe diabetics the threshold value is raised and glycosuria may cease before normal threshold values have been attained.

SUMMARY

A brief description of the technique of the glucose tolerance test has been presented along with the interpretation of results obtained when the test is used as an aid in the diagnosis of diabetes mellitus.

ACKNOWLEDGEMENT

We wish to extend to Dr. W. R. Campbell our wholehearted thanks for his aid and encouragement in the preparation of this paper.

PRIMARY ATYPICAL PNEUMONIA: ETIOLOGY UNKNOWN

There have been an increasing number of reports of a variety of pneumonia that is not due to pneumococcus. This pneumonia appears to be a disease of young adults primarily; and to be of an infectious nature. Thus it can readily be seen that it might assume major importance, especially in war time with so many young people being brought together in the living conditions of the armed forces. Colonel Warner states that it is the most communicable disease at Camp Borden. Further the ratio of atypical pneumonias to bacterial pneumonias is twenty to one to-day. For these reasons we have reviewed the literature and are presenting our views gained from this study.

PART I

CLINICAL ASPECTS—W. T. W. CLARKE

Definition

This atypical pneumonia may be defined as a clinical syndrome, characterized by a paucity of physical signs in the presence of marked pulmonary change as shown by X-ray, and not due to any of the previously known causes of pneumonia.

Terms

The terminology is that recommended in the official statement of the United States War Department. The terms that have been given the condition are very numerous and this has caused considerable confusion. Some of the more common and interesting terms are virus pneumonia, acute influenzal pneumonia, grip, acute pneumonitis, acute infection of the respiratory tract—variety X, and soldiers' pneumonia.

History

With the reporting of numerous cases and epidemics during the past eight years, a great deal of attention has been focused on this syndrome. It is difficult to analyse cases reported before this period because although the clinical, pathological, or even X-ray picture may be carefully described; cases with both clinical and X-ray descriptions are not easy to find. However,

cases described at the end of the 19th century and during the last war certainly may be the same conditions. It must also be admitted that the incidence of the disease has been much higher during the past eight years than can be explained by the increased awareness of the condition, the wider use of X-ray, or the effect of sulphonamides on pneumococcal pneumonias.

Predisposing

Epidemics have been chiefly amongst adolescents and young adults, but sporadic cases occur at all ages. Some interesting epidemics that resemble this picture have occurred amongst infants. There are no known important predisposing factors. The number of cases that are preceded by a common cold is small if careful distinction is made between a preceding attack of coryza and the upper respiratory infection believed to be due to the same agent as the pneumonia.

Onset

The onset of the illness is more gradual than that of pneumococcal pneumonia or influenza. In army camps and schools where there is no economic factor and the early reporting of any illness is encouraged, the usual duration of symptoms be-

fore reporting is 1 to 7 days. However some observers report that 25% of their cases came on in less than 24 hours.

There are two types of onset of this syndrome. The one may be described as the "flu" type of onset; and the other as the "respiratory" type. As the former is the commoner and yet the more difficult to diagnose, I am going to base my clinical description chiefly on such cases. In these cases the signs and symptoms may be divided into two groups, thus stressing the general nature of the infection. The respiratory tract involvement is only a feature, though, of course, the most prominent one, of the general infection. This is a characteristic of many virus diseases.

The EARLY SIGNS AND SYMPTOMS are general and do not even point to the respiratory tract as the site of disease.

Fever is constant, the average temperature being about 102°F. It is intermittent in type in contrast to pneumococcal pneumonia. In some cases it is up in the morning and down in the afternoon. Numerous observers have reported cases picked up early in which there were two temperature peaks, with an interval of a few days with lower temperatures. This is said to be a characteristic of virus infection. The fever goes by lysis.

Malaise also is practically constant. Generalized muscular pains are common but there is not the severe pain in the lumbar region and legs that is found in influenza. The general malaise is out of proportion to the appearance of well being of the patient.

Headache is very common. It varies from mild to severe, but it is the large number of patients with severe headache that is so striking. There is no evidence that it bears any relation to the encephalitis that has been reported with some cases of the pneumonia.

Chilliness, sometimes alternating with feverishness is common but actual chills are exceedingly rare.

Profuse *sweating* has not uncommonly been noted as a feature of the disease. In the mild cases the *heart rate* does not increase in proportion to the temperature, that is, there is a relative bradycardia.

Gastro-intestinal complaints are not a feature of this disease. Vomiting may occur but distension does not. Herpes also is unusual.

The *white blood count* is usually normal at first, although some series of cases have shown a definite leucopenia. There is often a slight rise later on. Some observers report a relative lymphocytosis while others have failed to find this.

I would like to draw attention again to the fact that all the signs and symptoms discussed so far have been of a general nature. You could have all of this picture yet no suggestion that the cause lay in the chest.

The SYMPTOMS AND SIGNS SUGGESTING RESPIRATORY TRACT INFECTION are superimposed on those of a general nature.

Cough occurs in 80% or greater of cases but does not appear until several days after the onset of the illness except in the "respiratory" type of onset when it is early. In some cases it is the most distressing, and most persistent symptom.

Sputum is absent or scanty at first but later becomes more copious and mucopurulent. It may have streaks of red blood in it, but "rusty" sputum never occurs.

Mild *injection* of the nasal and pharyngeal mucosa occurs in 25 to 50% of cases. The patient may complain of congestion of the nose or a sore throat often only noted on swallowing. This is one of the earliest features of the disease. There are no *physical signs in the chest* at the

time of hospitalization in over 75% of epidemic cases. Later on signs do occur in a very high percentage of cases. Slightly diminished air entry is said to be the earliest sign. The most frequently found sign however is rales. These appear some time after hospitalization yet may be extremely persistent once they do develop. They often disappear in one area and appear in others. Signs of frank consolidation are rare.

A dull *retrosternal ache* or sensation of tightness is so common as to be an important feature of the disease. True pleuritic pain is rare but signs or pathological evidence of involvement of the pleura are not so uncommon in severe cases.

X-ray findings are of the greatest assistance in diagnosis though there is no characteristic or pathognomonic picture. The feature common to them all is a transient consolidation where the physical signs would not lead you to suspect it. Indeed, some of the first reports of epidemics were by roentgenologists and these were probably responsible for awakening interest in the condition.

Three stages of the disease are recognized:

- (1) No evidence of pulmonary involvement.
- (2) Tracheobronchitis: accentuated hilar shadows and thickened bronchi radiating towards the periphery are seen.
- (3) Pneumonic.

The pneumonic picture is one of two general types. One is a homogeneous shadow, usually spreading out from the hilus, and oftenest toward the lower part of the chest but not rarely into an upper lobe. The shadow is not as dense as in lobar pneumonia and has not a definite margin nor a lobar distribution. The

other picture is patchy or mottled. Recognition of the three stages, and that the disease may stop at any one, is very helpful in understanding it. Over all types the changes are bilateral in 20% or more of the cases.

A characteristic of the *X-ray* appearance of the disease is the rapidity with which it may—indeed usually—comes on and changes.

Course

The course of the disease is that of an acute infection but it is quite variable. There are reports of cases picked up in routine *X-rays* of recruits who were apparently perfectly well. With these ambulant cases perhaps should be placed the cases of respiratory tract infection without lung involvement that are mentioned below. During some epidemics the disease has been characteristically brief. Figures of fever lasting 3-7 days, hospitalization 10 days, and disappearance of *X-ray* signs and complete recovery so that men can go back to any type of duty in three weeks are given. The usual order is for the fever to disappear before the patient feels well, and for the patient to feel perfectly well for some time before the rales and *X-ray* changes have disappeared. However, in other epidemics the course of the disease has been much more protracted. In a series of 100 cases from the R.C.A.F. centre at St. Thomas, Meakins reports an average stay in hospital of four weeks. After this a 7 day convalescent leave, then two weeks light duty were given. He points out that patients who have suffered from this usually mild disease become fatigued easily for a long time following recovery. In infants the epidemics reported have been of a more severe type with cyanosis and dyspnea a prominent feature, and a mortality of

20%. This is in marked contrast to the mild course and extremely low mortality of the epidemics reported from colleges and army camps.

Classification

Both epidemic and sporadic cases occur. It is found that a much higher per cent are severe and protracted among the sporadic cases. For this reason one who was just seeing the sporadic cases would think that the picture I have drawn underestimates the severity of the disease.

The syndrome has been divided into these two types:

- (a) Mild or epidemic form,
- (b) Severe or sporadic form.

This classification is clinically accurate. The disconcerting fact, however, is that in some carefully investigated outbreaks, one type of case appears definitely to have been contracted from the other. In the epidemic type there is strong evidence that the cases with lung involvement represent only a small percentage of a much more prevalent epidemic of upper respiratory tract infection. It is readily seen that the course is quite variable and any satisfactory classification can only be made on a basis of etiology.

Complications

Complete recovery and the absence of complications are said to be characteristic of this disease. In this respect it must be remembered that we are dealing with a comparatively new disease so that there has been little opportunity to follow up cases. One must not dismiss too readily the odd disconcerting case of a bronchiectasis that may have followed an attack of this type of pneumonia.

Diagnosis itself will have to be made eventually on the etiology. As this is impractical at the present time the best one can do is to diagnose the syndrome. This, in brief, is the typical story of the

gradual onset of a "general" illness with the features previously outlined, with absent or minor chest signs, and an X-ray showing marked pulmonary involvement. Signs and symptoms of chest involvement usually become added. In some cases failure of response to sulfonamides proves of considerable aid in diagnosis. A simple laboratory procedure showing a rise in the titre of cold agglutinins in this syndrome may prove to be of some aid in diagnosis.

The *differential diagnosis* may be subdivided into three general groups:

- (a) Non-pulmonary diseases that may be simulated by the general signs of this disease.

The type of 'flu (not influenzal pneumonia) that is so common is only distinguished in some cases by a chest X-ray or by more difficult laboratory procedures demonstrating the cause of the influenza. The number of cases in which X-ray changes in the lung have been found where not expected has proven surprising. With the onset of the signs and symptoms of chest involvement there is usually little difficulty if you are watching for an atypical pneumonia. It is readily seen how the gradual onset of general malaise, headache, cough, low fever, brachycardia and leucopenia might be confused with typhoid, especially where that disease is commoner. The differentiation is of course readily made if exposure, course and laboratory and X-ray investigations are considered.

- (b) Pulmonary conditions that are usually distinguished clinically. These are bacterial infections.

Bronchitis presents a somewhat similar story but the fever doesn't last over a week, the pulse is up in proportion to this fever, chest signs are more prominent, and bacteriological studies more fruitful.

A chest plate makes the distinction if and when the atypical pneumonia reaches the 3rd of the stages described under radiology. Typical pneumococcal pneumonia is readily distinguished. In connection with differentiation from this disease the sulphonamides have proven a two edged sword. By their rapid action on pneumococcal pneumonia and the lack of response of atypical pneumonia they have helped to differentiate and thus draw attention to the latter condition. On the other hand sulfonamides may have been given for a preceding cold, or very early but inadequately in the pneumococcal pneumonia, before the typical picture has developed; in these cases the typical picture may never develop at any stage. Rusty sputum, pleuritic pain, signs of consolidation, and especially recovery of pneumococci of types I, II, III, V, VII or VIII are of aid. This further emphasized the importance of determining the etiology wherever possible. Broncho-pneumonia due to the common bacterial causes may be simulated by atypical pneumonia but the careful investigation of the story, signs and bacteriology will again differentiate. The group of cases called unresolved pneumonia is gradually being whittled down. The introduction of lipiodol has placed many of them as bronchiectasis. It is now realized that certain cases that never had a typical history of lobar pneumonia yet on examination present the clinical picture of an unresolved pneumonia—both generally and locally—are actually cases of the clinical syndrome under discussion.

Tuberculosis in either a diffuse parenchymal or a chronic miliary form may be simulated exactly by the X-ray picture of a case of atypical pneumonia. Indeed, some of the earliest reports of this pneumonia were by radiologists stressing the

danger of diagnosing as tuberculosis, cases of involvement of the upper lobe by this type of pneumonia. If the differentiation is not certain on the history, physical, and sputum examinations; then a series of plates will show the more rapid variations in the atypical pneumonia. Lung abscess, bronchiectasis and bronchogenic carcinoma may all give hemoptysis and similar X-ray pictures and must be distinguished.

(c) Pulmonary diseases that cannot be distinguished clinically but only on their definitely known etiology. These are mostly non-bacterial.

The final group of diseases that require differentiation are some of the less common pneumonias that may present identical clinical and X-ray pictures. These are only differentiated because their etiology can be demonstrated. In some cases this requires tedious laboratory investigation. However, unless there is an epidemic of atypical pneumonia about, these other conditions should be eliminated by this method until we have some more certain method of diagnosing primary atypical pneumonia. These pneumonias are psittacosis, ornithosis and other even rarer ones due to viruses; Q-fever and others due to rickettsia; toxoplasmosis due to a protozoan; and coccidiomycosis due to a fungus.

Treatment

There is no specific therapy. Indeed the most important thing that can be said is not to use chemotherapy for it may do harm and cannot do any good. Of course there will be cases in which the diagnosis is not certain; in these, adequate doses of sulfonamide should be given for 48 hours and if no response ensues, they are then discontinued. Transfusions from convalescents, and deep X-ray therapy are two forms of

specific treatment that have been tried but not extensively enough for conclusive results.

In the supportive treatment, the non-productive cough must be controlled, lots of fluids given, an ice cap, oxygen if any dyspnea, etc. Aspirin is best avoided in those cases where sweating is marked. In the recovery stage, postural drainage and deep breathing exercises are of value. Although the convalescence must be prolonged, it may be better not to keep the patient right in a hospital bed just because there is an occasional rale; but rather to have them up, but see that they don't become fatigued.

Review and Conclusions:

1. A distinct clinical syndrome of a

pneumonia of recent importance is prevalent.

2. A brief note on its terminology and history is given.
3. The clinical picture and the variations of the syndrome are given. The pneumonias may represent only the occasional case in a widespread epidemic of upper respiratory tract infection.
4. Diagnosis and differential diagnosis are outlined.
5. Treatment is symptomatic; no sulfonamides.
6. The folly of naming or classifying pneumonia on any basis except one of etiology is seen.

PART II

AETIOLOGY AND PATHOLOGY—W. B. ARNUP

I. *Aetiology*

To discuss the aetiological factors of this syndrome it is necessary to make a distinction between epidemic and sporadic cases. Much investigation has recently been done on the more spectacular epidemic outbreaks. Yet routine chest X-rays and more careful examination of apparently mild upper respiratory tract infections have made us aware of pulmonary involvement occurring more frequently than formerly suspected. Although the following information is gleaned from the epidemic studies it is probable that it is equally applicable to the sporadic cases.

The epidemic variety presents a clinical syndrome that enables a diagnosis accurate enough to allow investigation as a definite entity. Indeed, some observers claim that this is a relatively new disease. From such studies the following observations seem justified.

(1) *The Geographic Distribution* suggests that it is widespread, cases having been reported from various centres in North America, the British Isles, Europe, and even tropical climates.

(2) *The Seasonal Incidence* is not characteristic and corresponds only roughly with other respiratory infections.

(3) *Sex and Race* apparently play no part as predisposing factors.

(4) *Age*—Predominately the outbreaks are among healthy young adults and adolescents. Yet similar epidemics in children are reported and cases have occurred between the ages of 4 to 80.

(5) *Epidemiology*—Reports that definitely trace the infection from person to person have established this condition to be contagious. The mode of spread is by direct contact probably by inhalation of droplet infection. The evidence strongly suggests the occurrence of a carrier state due to mild infection with no

pulmonary manifestations. In this connection the possibility of sporadic outbreaks arising from infections carried by animals, especially birds, should not be ignored.

Reports about the infectivity vary with different observers partly due to the fact that many contacts develop only minor manifestations that can only be recognized as infection by serum titre tests. A difference in causative agents might also explain this discrepancy. Certainly the incidence of severe infection with pulmonary signs is low, both in the general population and in the contacts in epidemic areas.

(6) *The Incubation Period* is roughly from ten to twenty-five days, with an average of eighteen days, but considerable variations in this estimate are reported. And yet the incubation period in any series that could be accurately traced appeared more constant for that particular outbreak.

(7) *Aetiological Agent*—Now we come to the ferretting out of the aetiological agent or agents responsible for this syndrome.

(A) Certain *clinical observations* that are consistently encountered point an accusing finger at a virus agent. These include:

- (1) The long incubation period
- (2) The relatively low communicability
- (3) The inability to find any causative agent consistently if at all
- (4) The inefficacy of chemotherapy
- (5) The pathological findings to be described later,

Further circumstantial evidence to support a virus can be obtained by considering known virus diseases. It is still impossible to isolate the virus in the majority of cases of any one of the proven virus diseases. The infecting of animals with the disease is extremely difficult. Such

virus diseases are usually manifested in children and young adults. The severity of individual infections varies considerably and they characteristically are rarely fatal.

(B) *Experimental Evidence* of a virus agent is not yet conclusive. A virus was first isolated from human respiratory infections in 1933 by the instillation of washings from the nasopharynx of clinical cases of influenza patients into ferrets. Many similar viruses have been isolated in various parts of the world by the same technique. Proof that this isolated virus was the causative agent was established when re-infection of humans occurred, at first accidentally from an infected ferret and then by instillation of the virus into human volunteers. Also convalescent serum neutralized the virus but serum taken in the acute stage did not.

But in 1936 and 1939 epidemics indistinguishable clinically failed to produce such a virus by the same technique. In 1940 a virus was isolated from a very limited epidemic again using the ferret and transferring the infection to mice. This was unlike the previously isolated strains but later virus neutralization tests by convalescent serum linked this virus to the epidemics of 1936 and 1939. The first isolated virus was called Influenza-A and the latter Influenza-B. Using the Jamaican mongoose workers have isolated a virus from definitely established cases of Primary Atypical Pneumonia that differs from the viruses of both Influenza-A and Influenza-B. Many recent similar attempts to isolate a virus from clinical cases have produced strains of viruses with striking similarity to each other and also to other known viruses. Thus there is a close relation between these recently isolated "Psittacosis-like" viruses and the

viruses of lymphogranuloma venereum, trachoma, inclusion conjunctivitis, psittacosis, and meningo-pneumonitis of mice.

The suggestion has been made that these all arose from a common parent strain but have been modified in passage through different hosts and tissues. In this regard it is interesting to speculate upon the relation of widespread virus infections in animals, especially among birds including domestic pigeons and fowl, to human infection. It is known that there is widespread latent virus infection in animals and that epidemics do occur especially in birds. It is also established that infections of atypical pneumonia in humans from sick birds have occurred. But these differed from true psittacosis in that intraperitoneal injection into mice did not cause death as psittacosis invariably has done.

Such studies would indicate that a number of strains of viruses are capable of producing the syndrome under consideration. The fact that a clinical picture indistinguishable clinically may be produced by the virus of psittacosis and the rickettsia of the Australian Q fever also suggests that the causative agent is not necessarily one specific virus. Recent investigation in this country especially in connection with military camps seems to substantiate this contention. It must be noted that these observations to follow were made on "influenza-like" outbreaks and not confined to cases of primary atypical pneumonia.

A widespread epidemic investigated in 1940-41 showed a proportion of cases to be due to Influenza-A by serological tests but no agent could be identified for the remainder of cases although they were identical clinically.

In an epidemic in 1941-1942 neither Influenza-A or B could be incriminated.

Primary Atypical Pneumonia was not a feature of either of these outbreaks.

But in 1942-1943 there were three distinct waves. In the *first* neither Influenza A or B were involved and 25% of these cases developed Primary Atypical Pneumonia.

In the second 23% were assessed to be due to Influenza B by serological tests and the remainder unidentified. Of all cases 26% developed atypical pneumonia although this was observed more often in the unidentified cases than in the ones shown to be due to Influenza B.

In the third wave in which no Primary Atypical Pneumonia developed the epidemic was very localized and shown to be due to Influenza-A.

These studies show that cases of Primary Atypical Pneumonia occurred during epidemics of respiratory infection. In all cases the clinical picture was identical except that in the outbreaks characterized by atypical pneumonia developing the onset was usually more insidious and Influenza A and B were not predominating. Even in such outbreaks it could not be determined clinically which cases were going to develop pulmonary signs that usually occurred after admission to hospital. During these epidemics 20-25% of febrile admissions developed chest signs.

It must be kept in mind, then, that these cases of Primary Atypical Pneumonia developed during epidemics of respiratory infections ranging all the way from sub-clinical infections to mild coryza-like symptoms, to short febrile infections, to the characteristic picture of Primary Atypical Pneumonia. This is a feature that has been obscured in other reports. Such findings are consistent with the discovery of so-called "Silent Bronchopneumonias" found on routine chest

X-ray and it is probable that a history of mild respiratory infection can be elicited in such cases.

(C) Discussion

It is probable that there is a virus infection of the mucosa of the respiratory tract that extends down the bronchial tree. It is a known fact experimentally that in a virus infection of the upper respiratory tract with no lung signs the titre for virus is as high in the lungs as in the turbinates for example. The mechanism for the production of the pneumonic changes is indefinite. There is the belief that the virus infection causes plugging of certain bronchioles by mucoid secretion producing local atelectasis and low grade infection by the normal flora. But both sputum culture and the limited observations from post-mortem lungs discredit this explanation but are consistent with the local reaction due to a virus.

If Primary Atypical Pneumonia is a complication of a more widespread virus infection of the respiratory tract why do *some* cases develop pulmonary manifestations while others do not? Also why are some *epidemics* more prone to develop pulmonic changes than others? Evidence for a specific pneumotropic virus is not yet conclusive. Perhaps the occurrence of pulmonary manifestations can be explained by differences in the individual's reaction to a virus infection influenced by pre-existing immunity or by the size of the infecting dose. The possibility of secondary infection by a *different* virus should not be overlooked as *secondary bacterial infection* is not a feature and may even be inhibited.

II. Pathology

Indeed, a characteristic of this disease is that it is rarely fatal. Yet some indication of pathological processes can be gained from clinical observation.

The changes occurring in the lung as determined by X-ray have been discussed in the preceding paper. Rarely is the pleura involved. Pericarditis has been reported but is rare. The kidneys are apparently little affected; albuminuria may occur at the height of fever and haematuria is extremely uncommon. Single reports of meningism, erythematous skin eruptions, and liver involvement as evidenced by slight jaundice have appeared. Although general manifestations occur the only significant pathological changes found in the limited observations thus far occurred in the lungs.

The bronchi showed a very reddened mucosa, the lumen containing abundant exudate reported as both pink and frothy or mucopurulent. On section they showed an acute interstitial bronchitis with infiltration of the walls with round cells and occasional polymorphonuclear leucocytes. The exudate also showed both polymorphonuclear leucocytes and round cells. Scattered throughout both lungs but especially in the lower lobes were patchy areas that felt like consolidation. On section these areas seemed to be filled with more fluid than exudate. The alveoli around the inflamed bronchioles were variably filled with exudate which was rather haemorrhagic and characterized by mononuclear cells in some areas and showing a tendency to organization in others. Alveolar walls were not broken down but were seen to be thickened and lined by large mononuclear cells. Elsewhere in the lung alveoli were filled with pink fluid and air.

Bacterial stains and inoculation of lung suspensions into mice and ferrets were negative.

Other findings reported were lesions simulating periarteritis nodosa in the pulmonary arteries and smaller radicles in

two cases and acute splenic enlargement in one.

The hilar nodes were not remarkable in any case. One interesting feature has been the finding of inclusion bodies in the lungs of infants dying during an epidemic of similar atypical pneumonia.

III. Summary

1. From epidemic investigations it has been established that this condition is contagious. The incidence factors and incubation period have been worked out.

2. The conclusion that the infection responsible for primary atypical pneumonia is in general a virus agent seems justified. Recent evidence suggests that the syndrome is a complication *or* a more severe manifestation of a more generalized infection of the respiratory tract.

3. It is possible that different strains of viruses, perhaps inter-related, are capable of causing this condition.

4. The pathological observations show a reaction in the bronchi, bronchioles, and surrounding lung tissue that is consistent with a virus infection although such has not been isolated from those sites.

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THE CHEMICAL TRANSMISSION OF NERVE IMPULSES

W. H. ALLEMANG, B.COM.

INTRODUCTION

The accumulated experimental evidence in respect to the transmission of nerve impulses between the nerve axon and the effector organ which it supplies has led to a chemical or "neurohumoral" theory of transmission. The theory holds that the nerve impulse brings about a response in the effector organ by the liberation of a chemical substance from the terminals of the nerve axon which acts as a major local exciting agent on the effector.

Much of the experimental work on the transmission of the nerve impulse has been done on nerves of the autonomic nervous system and the effectors which they supply. As a result of such evidence, it is now generally accepted that the liberation of a chemical substance is responsible for the mediation of the nerve impulse between postganglionic sympathetic and parasympathetic fibres and their effectors. From further experimental evidence, it is generally regarded that the transmission of nerve impulses in autonomic ganglia and from the motor end plate of a somatic motor nerve to skeletal muscle is chemical in nature. There is less evidence to support a chemical transmissive agent in the synapses of the central nervous system, although some investigators believe that this is so.

HISTORICAL APPROACH TO THE THEORY OF CHEMICAL TRANSMISSION OF NERVE IMPULSES

The first concrete proof of the mediation of nerve impulses by the release of specific chemical agents was the result of experiments conducted by Otto Loewi,

which were begun in 1921. Loewi's work had been anticipated by a number of Cambridge (England) workers from 1904-1914. In 1904, Elliot postulated the theory that sympathetic nerve impulses released small amounts of an epinephrine-like substance in immediate contact with effector cells. He had been led to this theory by the similarity between the effects of stimulation of sympathetic nerves and the injection of epinephrine. In 1906, Dixon suggested that on stimulation of the vagus nerve, a muscarine-like substance was liberated which acted as a chemical transmitter of the nerve impulse to the heart. He had been impressed by the similarity in effect between vagal stimulation and alkaloid muscarine on the heart. He concluded that "The excitation of a nerve induces the local liberation of a hormone which causes specific activity by combination with some constituent of the end organ." In 1914 Dale reinvestigated the pharmacological properties of acetylcholine. He was impressed by the relation of the action of parasympathetic nerve impulses and that of acetylcholine.

THE TRANSMISSION OF IMPULSES FROM PARASYMPATHETIC POSTGANGLIONIC FIBRES

(A) *The Evidence for a Chemical Mediator:*

The work of Otto Loewi begun in 1921 presented the first real proof of the transmission of nerve impulses by the release of chemical agents at the nerve terminals which produced a response on the effector organ. He showed that "when the vagus supply of an isolated perfused frog's heart

This article was judged to be the best essay submitted on a physiology assignment to III Year in 1943.

is stimulated, a chemical substance appears in the lumen of the ventricle which can be transferred to and produces a vagus effect on another ventricle." (Samson Wright, Ed. 7. p. 183.) The substance liberated from the first organ slowed the rate of the second. Loewi called this chemical "Vagus Substance" (Vagusstoff). In 1927 Rylant duplicated Loewi's experiment, using perfused rabbits' hearts.

Other investigators showed that a chemical mediator was instrumental in the transmission of excitation to other parasympathetically innervated structures.

- (i) Englehart (1931) showed that physiological stimulation of nerves also produces the chemical mediator. Impulses passing over the short ciliary nerves, produced by electrical stimulation or by reflex action induced by the exposure of the retina to light, liberated a substance having the properties of acetylcholine, in the aqueous humor of the eye.
- (ii) Dale and Feldberg in 1934 showed that the "Vagus Substance" was present in the perfusion fluid of the stomach of a dog whose vagi had been stimulated.

(B) *The Identification of Acetylcholine as the "Vagus Substance"*

Chemical examination of the "vagus substance" subsequently showed that it is acetylcholine since it met the following criteria:

- (i) It is a choline derivative inactivated by esterase and reactivated by acetylation.
- (ii) The hydrolytic action of the esterase is prevented by eserine.
- (iii) It is destroyed by hydrolysis in an alkaline medium but is not affected by boiling for several minutes in a slightly acid medium.

- (iv) Its action is blocked by atropine and curare.
- (v) The chemical mediator produces responses which bear a quantitative relation to one another in certain muscle indicators as does also acetylcholine.
- (vi) Both acetylcholine and the mediator are dialyzable and soluble in alcohol but not in ether.

Since both the chemical mediator and acetylcholine meet the above criteria, the "vagus substance" was identified as acetylcholine. Acetylcholine is believed to exist in the tissues in a physiologically inactive form which is not hydrolyzed by cholinesterase and does not diffuse. Under the influence of the nerve impulse the inactivated form is believed to be activated. It then diffuses, produces excitation and is then hydrolyzed by cholinesterase to choline and acetic acid.

Cholinesterase exists in the tissues in especially high concentration where acetylcholine is liberated by nerve impulses. The action of this enzyme in hydrolysis of acetylcholine is rapid, thus the effect of acetylcholine is brief. The hydrolytic action of cholinesterase may be slowed by physostigmine (eserine) or prostigmine. This is achieved by "substrate competition" of these substances which do not inactivate cholinesterase but are hydrolyzed by it. As a result, the action of acetylcholine is prolonged and intensified. Nachmansohn and Marnay (1937, 1938) showed that cholinesterase exists in the tissues in high enough concentration to hydrolyze the acetylcholine liberated within the refractory period.

THE TRANSMISSION OF IMPULSES FROM SYMPATHETIC POSTGANGLIONIC FIBRES

(A) *Sympathin E and I*

Cannon and Uridil (1921) observed the release of an epinephrine-like substance

upon stimulation of the sympathetic hepatic nerves. This was later established as the transmitter of excitation initiated by sympathetic nerve impulses at neuroeffector junctions. Cannon called this substance "sympathin." This substance is similar to epinephrine (adrenaline) in some respects but differs in others. Both substances when injected into the body have two actions, exciting certain tissues (accelerates the heart) and inhibiting others (the intestine). In the case of sympathin the two actions are separable. If the sympathetic nerves of a tissue excited by sympathetic impulses are stimulated, the sympathin released possesses only excitatory activities. Sympathin differs from epinephrine in failing to stimulate the dilator muscle of the iris.

Cannon and Rosenblueth (1933) were led to postulate the existence of two forms of sympathin. The excitatory form they designated as sympathin E, the inhibitory form as sympathin I. They postulated a theory that a chemical mediator M is released by sympathetic nerve endings under the influence of a nerve impulse and combines in the effector cell with a substance H. The H substance exists in two forms, an E form if the effector cell is excited, and an I form if it is inhibited, by sympathetic stimuli. Thus MH has two forms, ME (sympathin E) and MI (sympathin I). Sympathin E is formed in the heart and blood vessels, sympathin I in the intestine, urinary bladder, bronchi, etc.

There are certain objections to this theory. Sympathin I has not been shown to exist alone, but organs which are inhibited by sympathetic impulses contain blood vessels which receive excitatory sympathetic impulses, and it may be that the two types of sympathin are liberated on sympathetic stimulation. It has also been suggested that the two forms of

sympathin are in reality two forms of epinephrine and are not produced as two forms in the effector cells. Gaddum *et al.* believed that sympathin existed in only one form, capable of excitation or inhibition, depending on the tissue activated. In spite of these objections, however, no other explanation coincides as well with the experimental observations.

(B) *Acetylcholine as the Transmitter of Impulses of Certain Postganglionic Sympathetic Fibres*

The responses of sweat glands and certain blood vessels (e.g. supplying the skin in the face) are modified by parasympathetic drugs, but are supplied by sympathetic nerve fibres. This presented difficulties in the theory of sympathin as the chemical mediator of impulses in postganglionic sympathetic fibres. Dale and Feldberg concluded, however, that impulses from these nerves are transmitted by acetylcholine and the nerves involved are functionally comparable with parasympathetic postganglionic nerves.

THE TRANSMISSION OF NERVE IMPULSES IN AUTONOMIC GANGLIA

The theory of the mediation of nerve impulses by a chemical substance has been extended from autonomic postganglionic fibres to autonomic ganglia. It is believed that the ganglion cells are stimulated by release of acetylcholine by the terminals of the autonomic preganglionic fibre when a nerve impulse reaches the synapse. The evidence for this has been obtained largely from study of sympathetic ganglia, but there is reason to believe that it holds also for parasympathetic ganglia. Most of the studies of this problem employed an isolated and perfused sympathetic ganglion (superior cervical). After stimulation of preganglionic fibres, the perfusate was tested for acetylcholine. It was also

found that the ganglion cells were discharged by injecting small amounts of acetylcholine into the perfusion fluid. Thus all preganglionic nerve impulses, sympathetic and parasympathetic, stimulate ganglionic cells through the release of acetylcholine at the synapse. This is known as the Kibjakow-Feldberg theory of ganglionic transmission.

THE CHEMICAL MEDIATOR OF NERVE IMPULSES CAUSING THE SECRETION OF EPINEPHRINE

The cells of the adrenal medulla are innervated through the splanchnic nerves. These are preganglionic sympathetic fibres coming directly from the lateral horn cells of the spinal cord. This unusual phenomenon is explained from embryological considerations. The secreting units of the adrenal medulla are modified neuroblasts and are anatomically homologous with sympathetic ganglion cells. When the splanchnic nerves are stimulated in an eserinizated animal, acetylcholine as well as epinephrine is found in the venous blood leaving the adrenal gland. Thus acetylcholine is believed to be the mediator of nerve impulses causing the secretion of epinephrine.

THE CHEMICAL MEDIATOR OF NERVE IMPULSES AT THE NEUROMUSCULAR JUNCTION IN SKELETAL MUSCLE

Dale, Feldberg and Brown have presented evidence to show that when the motor nerve to skeletal muscle is stimulated under proper experimental conditions, acetylcholine can be found in the the perfusion fluid.

In addition, when small amounts (2 micrograms) of acetylcholine are injected into the artery of a properly prepared and isolated muscle, a twitch qualitatively similar to that obtained by electrical stimu-

lation of the motor nerve is produced. The extent and intensity of this response is increased by physostigmine (eserine). These facts are consistent with a theory of chemical transmission of nerve impulses to skeletal muscle.

Dale in 1939 concluded that "although many details of this complex problem require elucidation, it would appear that minute amounts of acetylcholine are liberated at motor nerve endings in skeletal muscle, and are concerned with the transmission of the excitatory process across the neuromuscular junction, and initiate the changes which result in muscular contraction." (Goodman and Gilman: *The Pharmacological Basis of Therapeutics*, p. 333.)

THE MEDIATION OF THE NERVE IMPULSE IN SYNAPSES IN THE CENTRAL NERVOUS SYSTEM

Those investigators who favor a theory of transmission of nerve impulses by acetylcholine in autonomic ganglia and skeletal muscle, are inclined to believe that it may be possible to show that a similar type of chemical mediator exists in synaptic transmission in the central nervous system. At present, the evidence for this is somewhat meagre, but results suggesting such a condition, have been obtained.

Nachmansohn has made investigations on the esterase power of various locations of the cerebrospinal axis. Mann, Tennenbaum and Quastel (1938) have shown that nervous tissue alone is capable of synthesizing acetylcholine in vitro. Chute, Feldberg and Smyth (1940) showed that acetylcholine was released in the perfusion fluid flowing through an isolated cat's brain. In 1940, Miller and co-workers showed that acetylcholine when applied to the eserinizated motor cortex of the cat elicits a response.

OBJECTIONS TO THE THEORY OF CHEMICAL TRANSMISSION OF NERVE IMPULSES

One of the chief objections to the theory of chemical transmission of nerve impulses is the necessity of accounting for the time relations between nerve stimulation and effector response. This period must be sufficient to allow liberation, diffusion, action, and destruction of the chemical mediator.

In the case of the autonomic nerve supply of the viscera or heart, the interval (about 100 milliseconds) is long enough to be compatible with the theory of chemical transmission. In autonomic ganglia, the interval is much smaller, being 2 milliseconds or less. Some claim that a slow transmitter, which is chemical, acts in the case of postganglionic autonomic fibres to viscera, and that a rapid electrical transmitter acts in autonomic ganglia and skeletal muscle.

Eccles in 1937 conceded that acetylcholine increases the excitability of ganglion cells. But he contends that "cholinesterase could not destroy the acetylcholine quickly enough to account for the rapid decay of the "synaptic transmitter indicated by his observations" (Forbes: *Journal of Neurophysiology* 1939, p. 467). Furthermore, in his experiments eserine (which protects acetylcholine from hydrolysis by cholinesterase) failed to prolong the action of the transmitter.

In response to these criticisms other evidence is available:

- (i) Rosenblueth and Simeoni (1938):
Showed that with larger doses of eserine, the decline of the transmitter of nerve impulses is measurably retarded.
- (ii) Feng and Ting (1938):
Showed that in skeletal muscle, the concentration of cholinesterase

is greatest at the neuromuscular junction. Moreover, this concentration of cholinesterase is adequate for the rapid destruction of acetylcholine required by the chemical theory of transmission.

- (iii) Rosenblueth and Morison (1937):
In experiments on the transmission of nerve impulses at the neuromuscular junction of skeletal muscle, they showed that the effects of curare, eserine and fatigue present difficulties in explanation on the basis of an electrical theory of transmission of nerve impulses. The effects of these factors are, however, readily explained on the basis of mediation of nerve impulses by acetylcholine.
- (iv) Cannon and Rosenblueth (1937):
Achieved similar results to Rosenblueth and Morison (above) from experiments on the cervical sympathetic ganglion which reinforced the chemical theory as applied to the synapse between neurons.

CONCLUSION

Thus, while there are certain objections to the theory of chemical transmission of nerve impulses, it seems that the experimental evidence available is best explained on the basis of a chemical theory of transmission. The transmission of nerve impulses from postganglionic fibres, both sympathetic and parasympathetic, to their effectors by means of a chemical mediator is generally accepted.

The transmission of nerve impulses in autonomic ganglia and at the neuromuscular junction of skeletal muscle by chemical means is not as yet universally accepted. Certain investigations favor a theory of electrical transmission. Forbes (A. Forbes: *Journey of Neurophysiology* 1939 p. 469) suggests that the chemical and

electrical theories of transmission of nerve impulse may not be entirely contradictory and may eventually be comparable with the wave and corpuscular theories of light. It would appear, however, that the chemical theory of transmission of nerve impulses in ganglia and skeletal muscle, is the more favored in the light of experimental evidence.

In regard to the transmission of nerve impulses in synaptic junctions in the central nervous system, it must be admitted that the experimental evidence of such is rather meagre. There is, however, some reason to believe that the mediator here is chemical, and is probably acetylcholine.

On the basis of the evidence for the chemical transmission of nerve impulses, Dale has made the following classification:

(1) *Cholinergic Nerves*: All nerves whose impulses are mediated through the release of acetylcholine:

- (i) postganglionic parasympathetic fibres.
- (ii) splanchnic nerves: preganglionic sympathetic fibres to the adrenal medulla.
- (iii) postganglionic sympathetic fibres to sweat glands and the blood vessels to the skin of the face.
- (iv) autonomic (sympathetic and parasympathetic) preganglionic fibres.
- (v) motor nerves to skeletal muscle.

(2) *Adrenergic Nerves*: Nerves whose impulses are through the release of epinephrine-like substances (sympathin).

- (i) All postganglionic sympathetic fibres except those to sweat glands and to the blood vessels of the skin of the face.

CLINICAL APPLICATION

"The concept of transmission of nerve

impulses to skeletal muscle by acetylcholine has opened up a new field of therapy for certain myopathic disorders." (Goodman and Gilman, p. 342.)

One of the most striking of these conditions is myasthenia gravis, a condition marked by extreme muscular weakness. The action of drugs on this disorder is correlated with the theory of chemical mediation of somatic motor nerve impulses by acetylcholine.

The pathological physiology of myasthenia gravis could be due to either:

- (i) A deficiency of acetylcholine produced at motor nerve endings, or
- (ii) An increase in muscle cholinesterase, or
- (iii) The existence of an abnormal substance or metabolite with a curare-like action which elevated the threshold of the muscle to the effects of nervous stimuli.

Injections of eserine or prostigmine return the strength of the muscle to normal. Prostigmine is the more effective drug but apparently adaptation to both of them occurs. As a result, a "prostigmine holiday" of one day in ten is sometimes given to those suffering from this condition by injection of prostigmine.

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MEDICINE I

Spontaneous Mediastinal Emphysema

D. S. Munroe and G. A. C. Webb
C.M.A.J., 48:3:232

This paper, complete with a case history, was written to stress the spontaneous nature of this condition and the importance of its correct diagnosis since it is a relatively minor ailment compared to those with which it is confused.

The condition may arise during strenuous effort or while asleep. It occurs in the absence of demonstrable lesions within the chest. Due to spontaneous origin this condition must be kept in mind when any patient of either sex from infancy to old age suffers pain in the chest, dyspnea or cyanosis.

The chief signs and symptoms are:—

1. Pain or sense of constriction over the sternum or praecordium which may radiate to the neck or back and is generally eased by rest.
2. Dyspnoea and cyansis (more frequently found in young children).
3. Hammon's sign—a rough cracking sound, synchronous with the heart beat, heard over a small area about the cardiac apex most clearly when the patient is in the left lateral position.
4. Reduction of the area of cardiac dullness and distant heart sounds.

The authors stress the importance of negative information regarding the history of previous disease of the lungs or

the cardiovascular system and the positive finding of air in the anterior mediastinum by lateral and oblique chest plates.

The most probable cause of this condition, the paper points out, is rupture of peribronchial alveoli allowing air to dissect its way along the pulmonary vessels and bronchi to the lung root and mediastinum, the pressure giving rise to the dyspnoea and cyanosis.

The differential diagnosis include angina pectoris, coronary occlusion, pleurisy and spontaneous pneumothorax. Although pain is common to all these conditions a normal electrocardiogram, temperature and sedimentation rate will enable one to determine the correct diagnosis.

The prognosis in adults is very good, the attack clearing up in about 10 days. However, many patients have a history of recurrences. The prognosis in infants must be guarded for death may ensue.

Treatment apart from rest in bed is symptomatic and directed towards the relief of pressure, especially in children.

MEDICINE II

Prophylactic Treatment of Rheumatic Fever by Sulfanilamide

Caroline B. Thomas

Bulletin New York Acad. Med.
Aug., 1942, 18:8:508-526

Though the causative agent of rheumatic fever has not yet been accurately

determined, there is much evidence to indicate that acute attacks of the disease are preceded by some infection with β -haemolytic *Streptococcus*. Yet treatment of the acute disease with sulfonamide has been found ineffective.

However, as the first attack of the disease is rarely fatal and seldom damages the heart enough to impair its function permanently, the author considered that it was important to prevent subsequent attacks and that this could be done by preventing the antecedent infection with β -haemolytic *Streptococcus*. Thereupon she began a study of the prophylactic effect of daily doses of sulfanilamide. Starting in 1936 55 young adults and adolescents who had had rheumatic fever within 3 years were given sulfanilamide in daily doses ranging from 15 to 20 grains from October to June. A similar group of 67 young people were observed as controls. In the period 1936 to 1940 not a single attack of major rheumatic fever occurred in any of the groups on drug therapy, yet 10% of the control group suffered rheumatic episodes. In addition when sulfanilamide was withheld from one of the treated group that individual became susceptible once more to rheumatic recurrences.

Believing the results statistically significant the author proceeded to a further follow-up without a formal control group. She now has had the opportunity of observing 19 patients who have taken sulfanilamide for 3 or more years. All are well and able to work hard. From her experience she considers it wise to begin the drug a few days to a week before discharge from the hospital after the first acute illness and to administer it the year round since rheumatic occurrences may come at any season. And since the greater part of recrudescences may come

within 5 years of the initial attack, she feels that 5 years should be the shortest period of drug therapy.

At the time of writing (1942) there had been 2 cases of recurrence of rheumatic fever in prophylactically treated patients. One was a case of pure chorea without previous Streptococcal infection, the other a mild but true attack of rheumatic fever. From the first case the author questions the effectiveness of sulfanilamide prophylaxis in the choreic variant of the rheumatic state.

A review of the American literature reveals that for a total of 648 patient-seasons there were less than 1% of rheumatic recurrences. Yet in control groups recrudescences have been noted in from 12 to 35%.

Toxic reactions take the form of nausea, rash, fever, leucopenia and very rarely agranulocytosis. The author finds that they are less likely to occur when smaller doses are employed. When they occur the drug should be stopped, and resumed several weeks later at a dose of 0.3 grams a day; this dose may gradually be increased to the desired total dose after several more weeks. A number of workers have observed a gradual lowering of the total white count during the first weeks of treatment sometimes to levels between 2500 and 4500 with subsequent increase to normal without discontinuing the drug. The granulocytes may not be depressed or may fall to 25 or 30%. Since agranulocytosis does rarely occur, however, the development of leucopenia must be watched for with the greatest care so that the drug may be discontinued whenever an abrupt decrease in leucocytes takes place. All the available reports of agranulocytosis following sulfanilamide administration for any reason are reviewed, of 27 cases, 15 were fatal, 12 recovered.

It is striking that none occurred before the 14th or after the 49th day of therapy and all but 2 took place within 3 weeks' time. Agranulocytosis appears at about the same time interval whether the drug has been taken continuously or intermittently and irrespective of the size of dose. It is therefore recommended that repeated leucocyte counts be done from the 2nd to the 7th week of therapy. The author feels that the risk entailed in giving sulfanilamide is so much less than the chance of serious rheumatic heart disease developing if treatment is withheld, that, providing proper precautions are taken, it must be disregarded.

SURGERY I

High Altitude Frostbite

Loyal Davis, John E. Scarff, Neil Rogers
and Meredith Dickinson

Surgery, Gynecology, and Obstetrics,
December, 1943

In this preliminary report, the authors point out the differences between this type and ordinary types of frostbite, differences due to (1) the extreme degrees of cold involved, (2) the brevity of exposure, (3) the augmentation of the effects of cold by anoxaemia and ischaemia.

Unlike ordinary freezing, high-altitude frostbite shows a striking predilection for the extremities, especially the fingers. The authors describe three clinical types: (1) mild, (2) severe—(a) wet, (b) dry.

Mild—The exposure is very brief, a minute or two. The fingers are waxy white, stiff, numb, painfully cold, and insensitive to touch. Microscopic examination shows absolutely no blood in the cutaneous capillary loops. Thermocouples indicate a skin temperature of 4°-6°C. lower on the affected side. With

return to a normal environmental temperature at this stage, no permanent anatomical change results.

Wet—With more prolonged exposure, multiple small blisters form on the affected parts, and coalesce rapidly to form huge blisters. Unlike simple vesicles, these consist of fluid *in the tissues*. The fluid may be clear or sanguinous. As it accumulates, it dissects away most of the epithelium, including much of the germinal layer, forming casts of the finger tips, and slow re-epithelialization of the surface must take place, from the remaining patches of germinal epithelium, giving a thin, tight, shiny, fragile skin. Sensory and sympathetic nerve function, including sweating and vascular control, are slowly re-established over a period of months or years.

Dry—This is due to the most severe exposure of all. It is like the wet type at first, but instead of going on to vesicle formation, the skin assumes a tense "ground-glass" appearance, the deeper tissues become dark and discoloured, and mummification of the finger results.

The selective action of high-altitude frostbite on the extremities, as opposed to the face, and other flat surfaces, is thought to be due to a difference in the mechanisms of production of this and other types of freezing, such as ordinary frostbite, and "immersion leg." It is thought that the results are produced by a local anoxaemia due to ischemia, due in turn to intense peripheral vasoconstriction produced almost immediately, by the exposure of a small part with a large surface area (the finger) to temperatures as low as -50°F. Microscopic examination has actually shown this vasoconstriction, which may last for 24 hours or more. The lesion is damage to the intima of the terminal capillary loops. If the exposure is bad enough,

thrombosis occurs at the arteriolo-capillary junctions, causing gangrene. In less severe cases, the vessels are damaged similarly, but if the spasm passes before thrombosis occurs, the tissues are flooded by transudate, and vesicles form.

Treatment: (a) preventive—reduction of exposure is a matter for engineers and aviators to solve. Protective ointments have proved ineffective.

(b) curative. All methods are directed towards producing vasodilatation. Heat is suggested, but the problems of how much, how soon, and how long to apply it, are not yet solved. Greene has suggested a method of refrigeration of the affected parts at temperatures a little above freezing, to reduce the metabolic requirements to a level which the circulation remaining can meet. The authors give their reasons for doubting this logic, and state that in a controlled series of cases, they found patients allowed to keep their hands at room temperature had somewhat more blistering, but much less pain and restlessness than those treated by Greene's refrigeration method.

Other vasodilatory methods are discussed: (a) general heat, with local reflex vasodilatation; (b) direct antispasmodic drugs (amyl nitrite, alcohol); (c) indirect antispasmodics acting on the sympathetic system (mecholin); (d) injection block of peripheral nerves or sympathetic trunks. The only effective methods were found to be heat and sympathetic block, but these are of value only if administered before thrombosis has occurred, and in the absence of permanent capillary damage.

The paper is illustrated by excellent and abundant photographs.

H. K.

SURGERY II

The Diagnosis and Treatment of Sliding Hernia of the Sigmoid

Roscoe R. Graham, M.B.

Ann. of Surg., Oct., 1935

This uncommon occurrence, if met, and not recognized in the repair of a hernia, may have fatal results.

Nature—A hernia of large bowel from which the peritoneum has been partially stripped, passing through the internal ring. The sac is formed by parietal peritoneum of the wall lateral to the internal ring, and the lateral leaf of the mesentery of the sigmoid. The sigmoid colon lies mainly lateral to the sac and is attached to its wall. It is important to note that the blood supply of the bowel is distributed along this line of contact with the sac. Attempts to separate the sac from the colon thus deprive the bowel of its blood supply which leads to gangrene. It is seen therefore that only a portion of the colon is covered with peritoneum.

Diagnosis—(1) a hernia of long standing and increasing in size; (2) a truss which was formerly efficient can no longer be used because of pain and irritation; (3) hernia finally becomes irreducible, and attempts to reduce it are painful; (4) it seldom strangulates.

At Operation—(1) unusual amount of fat about the sac; (2) the thickness of the sac; (3) inability to return the contents of the sac to the peritoneal cavity; (4) absence of a crescentic border to the fundus of the sac; (5) unusual vascularity of the posterior portion of the sac; (6) on opening the anterior wall of the sac, the posterior wall of the sac is seen to continue up to the colon.

Procedure—The abdomen is opened with a paramedian incision and the sigmoid *drawn up* into the abdomen. The

incision made in the sac is then seen to be a linear slit in the lateral leaf of the sigmoid mesentery. This is closed by continuous suture. The inguinal canal is then repaired with a strip of external oblique fascia, or in recurrent or large types a strip of fascia lata.

The laparotomy does not prolong the convalescence and prevents damage of the blood supply vital to the sigmoid.

Author's Note: These herniae are of the indirect type and are usually accompanied by herniation of small bowel. The organ involved may be sigmoid or caecum, to either of which the urinary bladder may be added.

A. M. M.

PSYCHIATRY I

Psychosomatic Aspect of Medical Practice in Wartime

Edward Weiss, M.D., F.A.C.P.

Medical Clinics of North America
November, 1943

It has been estimated that 35 percent of patients consulting the average physician have no definite bodily disease to account for their symptoms and have or have had emotional disturbances which are entirely responsible for their complaints. An equal number have illness dependent partially on emotional problems and partially on organic disease, and the remainder (30%) have illness bearing no relation to emotional disturbance. The patients with symptoms dependent to any extent on emotional problems are quite commonly dismissed without careful treatment and come, consequently, under the care of quacks and irregular practitioners. Often the physician casts suspicion upon the organ or system of which the patient complains, with resulting enhancement of symptoms, since the unfortunate patient is

warned to be watchful for additional complaints. Overtreatment of a very minor condition will intensify a neurotic condition.

The neurotic person can be treated only from the psychological standpoint. In civil life, ill-health arises in a predisposed individual because of long-standing dissatisfaction in business, social or home life. The stress of war imposes further burdens upon such predisposed persons. Failure of adjustment is manifested by a disturbance of bodily function which may imitate any disease, or of mood which may appear as anxiety, obsession, depression, etc. Many physicians apparently do not realize that chronic illness involving prolonged physiological disturbance can be psychogenic. This fact may be attributed to the traditional teaching of medicine which tends to base all disease on a structural or physiological disorder. The diagnosis of functional illness must be established, not simply by the exclusion of organic disease, but on its own characteristics as well. In chronic illness, personality study is as important as laboratory analysis.

The physician must know the patient as a personality and not as a medical case only. The patient's confidence can first be established by taking a thorough history and making a careful examination with laboratory tests such as are necessary to exclude organic disease. Having assured the patient that there is no physical disease present, it is usually easy, by means of citing examples of psychic causes for physiological disturbance (blushing, goose-flesh, palpitation, diarrhoea) to make the patient understand that a disturbance of emotional life may be responsible for symptoms. Then, important clues to the disturbance may be found by encouraging a discussion of problems centering around voca-

tional, religious, marital and parent-child relationships. This is best accomplished by indirect questioning.

The author often tells his patients that, if they cannot find an outlet for tension of emotional origin by word or action, the body will find a means of expressing this tension through a kind of "body language." For example, if the patient has dysphagia for which no organic cause can be found, he tells him that there is something in his life situation which he "cannot swallow." Nausea indicates that some factor "cannot be stomached." This often appeals to the patient as a common-sense method of approaching the emotional factor in illness, even though it is not appreciated by the medically trained.

Sexuality and its relation to neurosis merit special comment. Difficulty in the sexual sphere appears as a revealing index to a neurotic personality and can be looked upon in that light. In this matter, Freud has been grossly misunderstood and misquoted. Varying degrees of frigidity and impotence serve as reliable indices to the kind of personality likely to develop a neurosis.

It is often of great assistance to the patient to know that there is no organic basis for his ailments and that the disturbance is emotional in origin. This usually gives him reassurance and prevents him from seeking further medical or surgical treatment or quackery, involving expense and inconvenience. Thereby discussing the problem involved will alleviate symptoms in some cases and frequently aid in the solution will help greatly.

The physician must be cautious in giving advice in solution of personal problems as this is dangerous to the patient and to himself. He should be able to deal with the less troublesome neuroses, however, and leave the major

neuroses to those especially trained in their management.

W. J. H.

OBSTETRICS AND GYNAEC- COLOGY I

A Consideration of Certain Factors Pertaining to the Control of Carcinoma of the Cervix

Norman F. Miller, M.D.

Ann Arbor, Michigan

American Journal of Obstetrics and
Gynaecology

Vo. 46, No. 5, Nov., 1943

In 1931 a Gynaecology Tumour Conference was instituted at Ann Arbor. The group has met twice a week since then and has studied 1876 malignant tumours of the female reproductive system. The malignancy of each of these has been proven by microscopic examination, and all of the cases have been followed up. The importance of carcinoma of the cervix is emphasized by the fact that of these cases 1235 (i.e. 65.8%) were carcinomata of the cervix, while the next largest group (263 cases of carcinoma of the fundus of the uterus) comprised only 14.1%.

The author reviews in a table the percentages of patients with carcinoma of the cervix surviving at the end of five years in various series from 1905 to its present series in 1943. While there are rather wide variations in the figures (due in large measure to the lack of a satisfactory system of classification of carcinoma of the cervix), yet on the whole the results do not indicate that much progress has been made in the treatment of this condition in the past twenty-five years.

The method of classification that is used at the University of Michigan Hospital is presented:

Group I—Very early cases, in which there is no clinical evidence of the condition but its presence can be proven histologically.

Group II—Cases in which the condition is recognized clinically but in which there is still no spread beyond the cervix.

Group III—Cases in which involvement of the parametrium is uncertain.

Group IV—Advanced cases.

In 66% of cases of carcinoma of the cervix the cause of death is uraemia, and/or impaired renal function caused by the encroachment of the tumour on the ureters or by scarring of the ureters. The lives of these patients might be prolonged by anastomosing the ureter with the intestine, or, in cases in which the tumour is causing obstruction of the intestinal tract, by a ureterostomy.

Since the chances of survival decrease by 16 to 20% per month after the onset of symptoms, it is of the utmost importance that the condition should be diagnosed as early as possible. To this end much money and effort has been expended in an attempt to educate the public; but, in spite of this, the number of cases discovered early is *not* increasing. This the author attributes to the fact that many women do not even know where the cervix is and do not understand the verbal instruction that has been given on the subject. The author has prepared a coloured film which he offers to physicians in the hope that with the aid of this they will be able to present the problem more clearly to their patients.

At the end of the article is a discussion by several other men. One of these, Dr. Edward Allen, suggests that women should be educated to expect and to demand an examination of their genital system as a *routine* measure, in order that cases of cancer may be discovered

early. He emphasizes the point that such examinations must *not* be begun at eighteen or twenty years of age, but must be made from childhood up if women are to overcome their aversion to examination of the genitals.

K.F.C.

PAEDIATRICS I

Acute Glomerulonephritis occurring in 3 children in the same family

A. B. Tudor, M.D.

Am. J. of Dis. of Children, Nov., 1943

Acute glomerulonephritis in siblings has been rarely reported. This is surprising in view of the high incidence of infections of the upper respiratory tract, the great contagiousness of these infections and the frequency with which attacks of acute nephritis are preceded by such infections.

This author reports acute nephritis developing in the youngest three of four brothers and sisters: John, aged 4 years, Marion and Margaret, twins, aged 3 years, and Mary, aged 5 years. Margaret had a mild upper respiratory tract infection for 3 weeks, greatly enlarged and injected tonsils and a bilateral cervical adenitis. Marion was lethargic with cervical adenitis, a swollen abdomen, periorbital edema, generalized lymphadenopathy and greatly enlarged and injected tonsils. John had a sore throat, cervical adenitis, fever and vomiting. Mary had an upper respiratory tract infection.

The four children were all seen at the same time and the youngest three diagnosed as and treated for acute nephritis. Each child was discharged from hospital at the end of three weeks. The children were examined at 2-week intervals. One month after discharge no child had any blood or albumin in his urine and all

phenolsulphonphthalein tests showed normal excretion. Five months later all four children had tonsillectomies and adenoidectomies, all made rapid recoveries and were discharged with normal urines.

The importance of this report is that only 2 of the 3 children had obvious glomerulonephritis and in the 3rd the diagnosis was made only by urinary and blood examination, i.e., all siblings of patients with acute glomerulonephritis should have urine examinations, and if such were done, cases without clinical symptoms would be picked up.

PAEDIATRICS II

Peptic Ulcers in Infancy and Childhood

Miriam C. Brenner, M.D.

J. of Paed., Oct., 1943

For many years it was thought that peptic ulcers in young children were so rare that they could be disregarded in diagnosis, but now the condition is coming to be regarded as of possible importance even in early infancy.

Ulcers in children fall into several groups:—

- (a) Ulcer of the newborn infant which is identified by melena and either heals rapidly or goes on to rupture or hemorrhage.
- (b) Ulcers in young infants which appear to have epidemic incidence and may be associated with exanthematous diseases.
- (c) Ulcers in children between 1 and 9 years of age which are of the adult type but do not produce typical symptoms.
- (d) Ulcers in older children which are entirely similar to those seen in adults as to both symptomatology and pathology.

Holt found that the greatest incidence of ulcer in childhood was between 6 weeks and 5 months of age, with 70% occurring in that age period; and only 10% in the neonatal period.

The etiology of ulcers is as unsettled in infants and children as in adults. Symptoms vary from complete absence to the typical syndrome as seen in adults. Pathologically, the ulcers seen in childhood are similar to those seen in adults.

Brenner reports 8 cases of peptic and duodenal ulcer seen in the course of about 500 routine autopsies on infants and children at the Colorado General Hospital during a six-year period. Two occurred within 3 days of birth; in the first no history was obtained, but the second had a rather definite clinical history of gastric symptoms. In 2 cases, ulcers were found in association with severe infectious disease of the central nervous system. Two showed only scars of previous ulcers, i.e. the ulcers occurred without symptoms and healed without specific treatment. Seven of these were duodenal ulcers, and one gastric.

BIOCHEMISTRY I

A Rational Approach to Chemotherapy

Paul Fildes

Lancet, 1, 1940, 955

The author presents a brief summary of the significant developments in chemotherapy up until the time of publication in which he shows that one view of sulphonamide drug action is inhibition of an enzyme system in which p-amino-benzoic acid is involved in some essential manner possibly as a coenzyme.

He gives a brief discussion of bacterial metabolism in order that you may understand just what "growth factors" are. He works on the premise that originally

all bacteria were capable of synthesising adequate foods for survival from elemental biological substances (i.e. CO_2 , O_2 and NH_3). By way of an example he can show by minimal media that *B coli* can synthesise protein from NH_3 and CO_2 whereas *B typhosum* cannot do this and protein is manufactured by this organism only when amino acids are added. Therefore, amino acids constitute a "growth factor" for *B typhosum*. It is also an essential metabolite for survival is impossible unless protein is manufactured.

Now if *B coli* is grown on an ammonia media, cozymase is formed. On the other hand *Proteus vulgaris* will grow only if cozymase is added or if nicotinic acid is added. It can therefore not synthesise nicotinic acid but can manufacture the rest of the molecule. *B typhosum* in contrast will not grow from the ammonia media but if amino acids are added, it will not only grow but produce cozymase also. The inference is therefore that it manufactures cozymase from the amino acids. *Staphylococcus* is still more dependant on its environment requiring both cozymase and amino acids for survival, while *H influenzae* can not finish the synthesis of cozymase given the nicotinic acid.

Fildes therefore draws up the following scheme:

$\text{NH}_3 \rightarrow$ Amino Acid
 Stage I
 $\rightarrow$ Nicotinic Acid
 Stage II
 $\rightarrow$ Cozymase
 Stage III

Stage I—growth factor for *B typhosum* and *Staphylococcus*.
 Stage II—growth factor for *Staphylococcus* and *Proteus*.
 Stage III—growth factor for *H influenzae*.



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These are therefore growth factors for the organism and as such by definition cannot be synthesised by the organism. They are at the same time essential metabolites to all the organisms mentioned.

With this outline of bacterial metabolism, the author discusses the modes of bacterial inhibition.

(1) In 1929, the author demonstrated that if the oxidising reducing potential of the culture was too high, regardless of adequate metabolites, growth would not occur. This was interpreted as interference by oxidation so that some metabolite when required to be reduced existed in the oxidised state thereby inhibiting metabolism.

(2) In another case, it was shown that existence of a sulphydryl ($-SH$) group was necessary to the existence of the organism (staphylococcus). If mercury was added, the organism was paralysed but growth could be reinstituted by addition of sulphydryl groups and in proportion to the sulphydryl groups added. Therefore the author postulated the formation of a reversible complex between the sulphydryl group and mercury.

(3) In the case of sulphanilamide, it was shown that p-amino-benzoic acid inhibited sulphonamides quantitatively. Sensitivity of the organism to the drug depends therefore partially on its ability to synthesise p-amino-benzoic acid which Fildes postulates is an essential bacterial metabolite. The relationship between the sulphonamide and the p-aminobenzoic acid does not appear to be a molecular one for no molecular ratio can be determined. This led the author to the theory that sulphonamide competes with p-amino-benzoic acid for its place in bacterial metabolism and the inhibition is therefore along the well recognised lines of competitive enzyme inhibition.

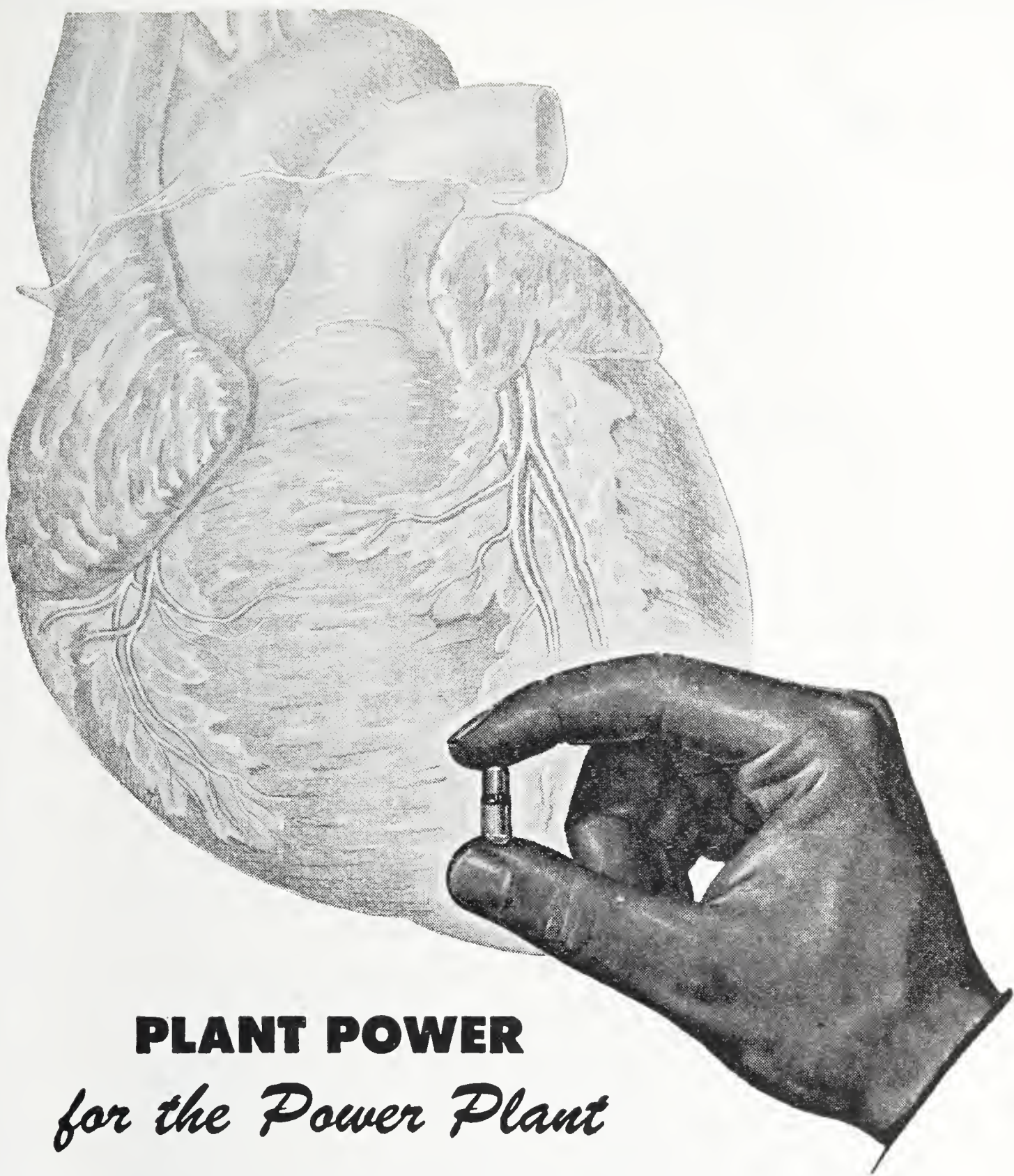
The author's general conclusions therefore are that generally speaking there are three methods of inhibiting bacterial growth:

(1) by oxidation of an essential metabolite;

(2) by inactivation of an essential grouping;

(3) by competitive of an indispensable enzyme system.

H. B. S.



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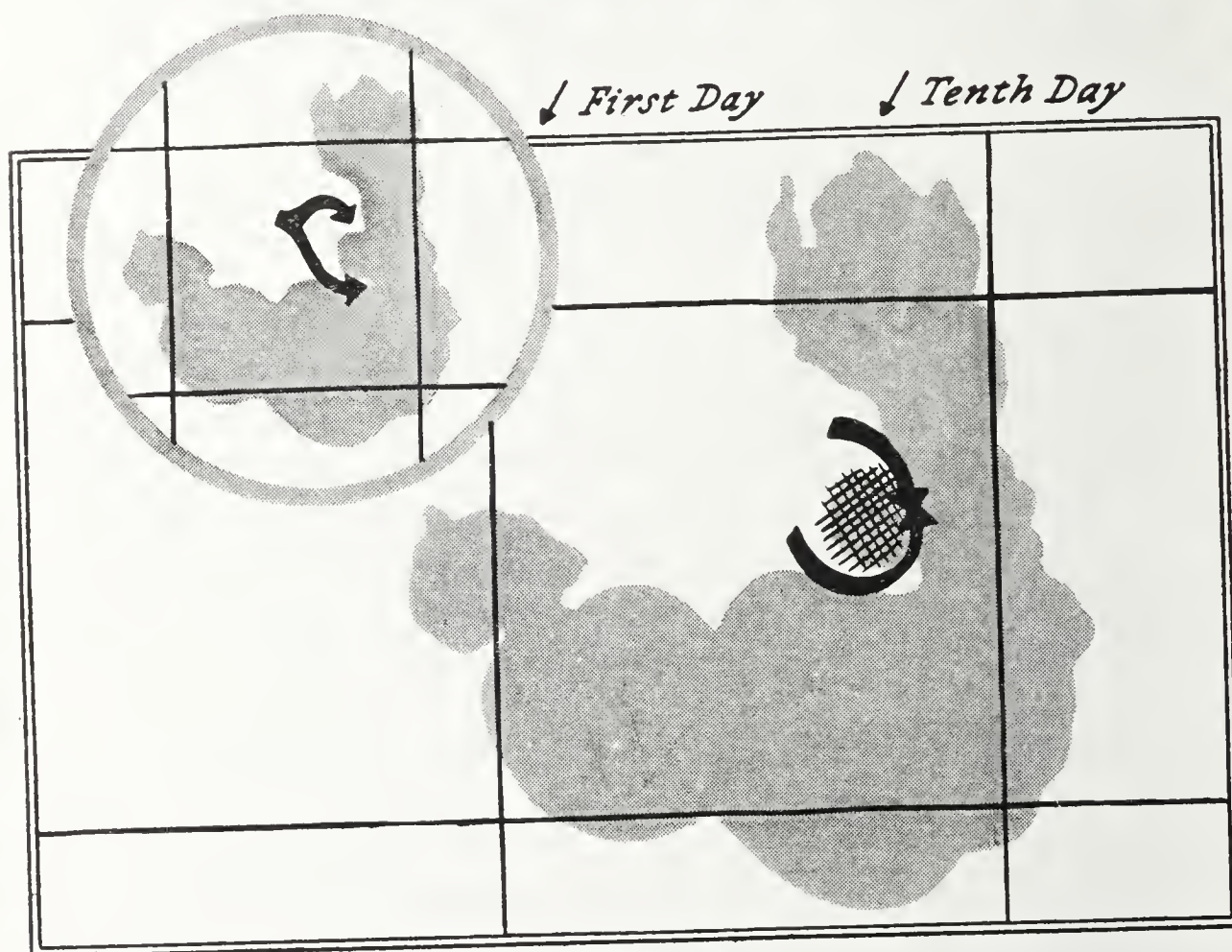
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*WOLDMAN, E. E. and POLAN, C. G.: The Value of Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer: A review of 407 Consecutive Cases, *Am. J. M. Sc.* 198: 155-164 (Aug.) 1939.

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